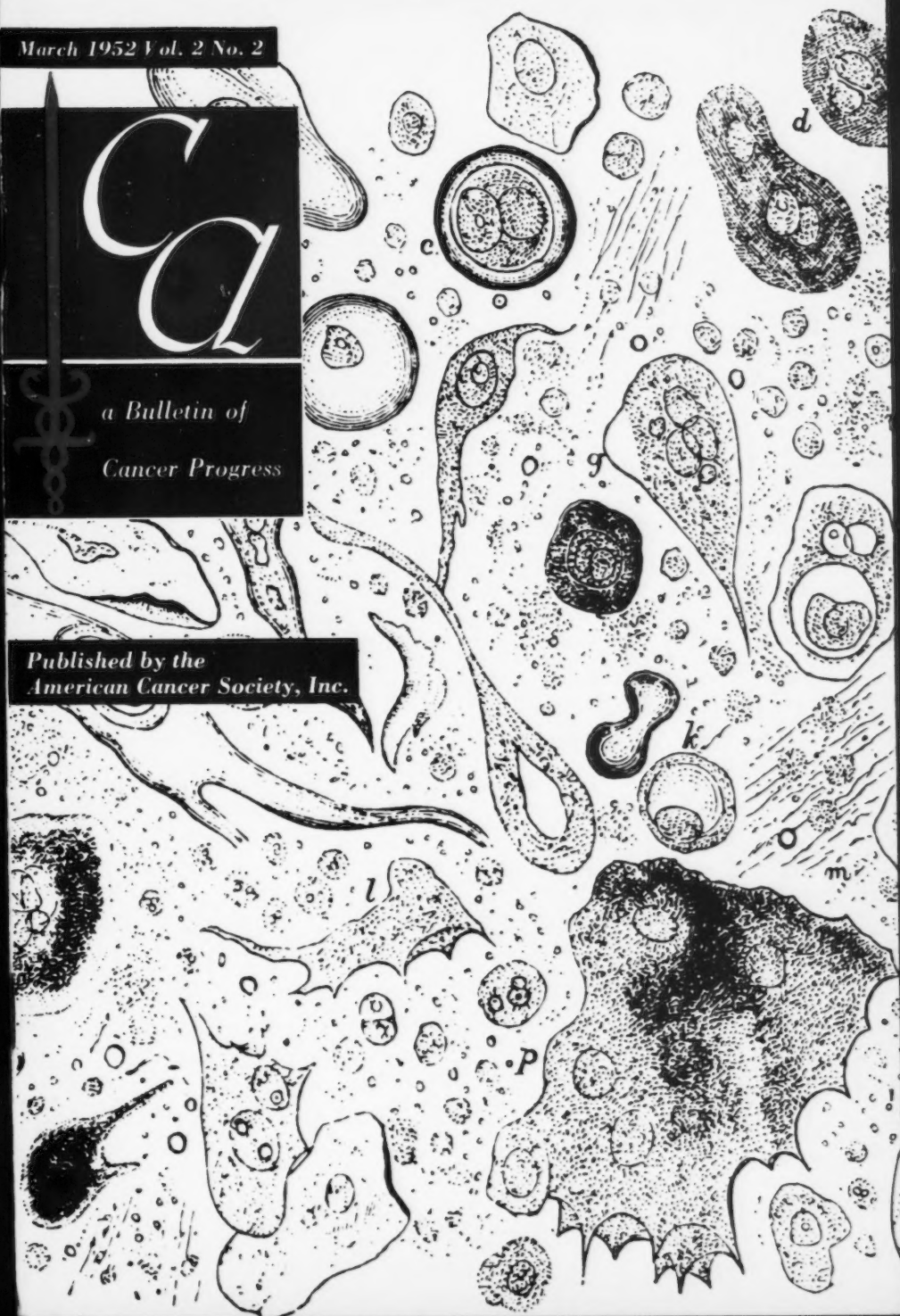


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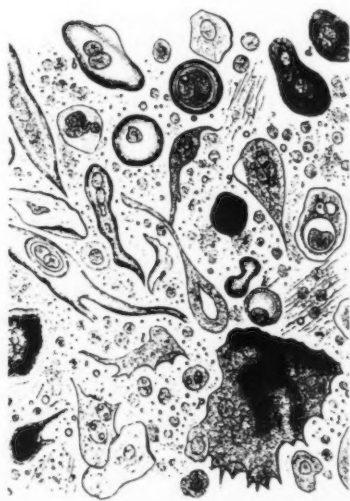
*an idea
whose time
has come*

Aulu-Gelle in Rome in A.D. 130 distinguished veins from arteries by the SPIRITUS NATURALIS (air) contained in arterial blood. A quarter century later, Galen described the aeration of the blood as taking place in the heart. Fifteen centuries later, Servetus accurately described the pulmonary circulation, seventy-five years before the immortal Harvey published his discovery. Similarly, Mendel's paper on inheritance in peas remained unnoticed until its rediscovery by DeVries thirty-five years later. A lapse of six years intervened between Pasteur's work on microbiology and its application to aseptic surgery by Lis-

ter. Twelve years elapsed between Fleming's discovery and, under pressure of war necessity, its practical application by Florey to the development of modern antibiotics. This period of hibernation or incubation is characteristic of all great discoveries. Each awaits its proper timing. "Invasion of armies, but not of ideas, can be stopped."

The early studies in cytology of Papanicolaou incubated for more than a decade. In the last ten years, however, applications have been made to several fields of investigation, none more important than that of the early diagnosis of cancer. As a contribution toward minimizing the dormant period, this issue summarizes the proceedings of a recent conference on Exfoliative Cytologic Diagnosis. In view of the urgency for early diagnosis of cancer, cytology is now undoubtedly an "idea whose time has come."

Probably the first person to identify cancer cells in a body fluid was Beale, from whose paper, published in the Archives of Medicine, 1860-61, is taken the woodcut of cells in the sputum in cancer of the pharynx.



NEWSLETTER

MARCH, 1952

CINCINNATI: YARDSTICK OF PROGRESS

The Second National Cancer Conference in Cincinnati served as a yardstick to measure advances in basic and clinical cancer research. Alongside abstracts from the First National Cancer Conference in Memphis three years ago, the Cincinnati papers showed that substantial progress has been made right down the line -- in every field of investigation. Noteworthy is the observation that many fundamental studies of three years ago -- investigations then presumably unrelated to the cancer problem -- now are yielding results that may have considerable clinical implications. Some of the highlights follow.

Lung: The rapid rise in lung cancer -- the rate has almost tripled in 20 years -- made panels concerned with this aspect of the disease well attended. Among the more encouraging reports on treatment was that of Hare (Lahey Clinic) and Trump (Mass. Inst. Tech.) who reviewed twenty-five generally advanced cases treated with two-million-volt x-ray and rotation therapy during the last two years. Their results: ten dead, fifteen living some up to twenty-four months after treatment. The field usually covers points of lymphatic spread. The investigators feel that the position of this type of therapy in treating lung cancer has been established.

McDonald (Mayo Clinic) reported that men outnumbered women in all types of bronchogenic carcinoma: 29:1 in small-cell types and 5:1 for squamous, large-cell, and adenocarcinoma. Survival, he said, was best in large-cell carcinoma. Ackerman (Wash. U.) cited evidence that bronchogenic cancer arises as islands of carcinoma in situ in most epidermoid and undifferentiated types. He warned that an invasive tumor almost always can be found nearby to indicate an aggressive therapeutic approach.

Anderson (U.S.P.H.S.) said 15 million small-film chest roentgenograms are made yearly by official and voluntary agencies and suggested that these be exploited by can-

cer control agencies. Guiss (U. South. Calif.) gave these significant figures on a survey: 1,867,201 chest films made in ten months; 3500 chest neoplasia suspects; cancer ruled out in 1537, confirmed in 240, metastatic in 89, goiter in 417, untreated clinically benign tumors in 206, treatment refused by 74, lost 108, and diagnosis pending for 829. He expressed the opinion that many of the untreated "clinically benign" tumors actually are silent cancers and, owing in part to delay, will kill the patients. He suggested that emphasis be shifted from cancers of accessible sites to hidden tumors, because he believes the latter are curable if found early. Overholt (Boston) reported that when treatment promptly followed discovery of silent tumors, all were resectable and 75 per cent showed no evidence of lymphatic spread.

Maier (New York) urged surgical exploration for suspected cancer of the lung. He pointed to the wide variation of results of cytological diagnosis as evidence of inaccuracy and inexpertness; and he asserted that bronchoscopy can show up no more than 10 or 15 per cent of the cases of early lung cancer. He commented on the fact that many lung cancers first are diagnosed as virus infection. Skavlem (U. Cincinnati) asserted that metastatic pulmonary tumors occur in numerous forms, and they must not be confounded with miliary tuberculosis, pneumoconiosis, sarcoidosis and other chronic granulomatoses, virus pneumonia, congestion, or edema.

Kent (Pittsburgh) described the use of radioactive colloidal gold in carcinomatosis of the pleura. Karnofsky recommended the use of nitrogen mustard as a palliative when patients are inoperable or there has been a surgical failure.

Lymphoma-Leukemia: Gross (Bronx V.A. Hospital) blueprinted a "working hypothesis" of leukemia: a virus transmitted from one generation to another, frequently without showing symptoms in its carrier hosts for a century or two. He outlined evidence supporting the hypothesis in chick and mouse studies (egg or embryonic extracts carried the virus -- and the older the animal the less susceptible it was to inoculated virus); and he asserted that if this be true in humans as well, individuals with tumor symptoms or leukemia would represent only a small fraction of those actually carrying the seeds of disease.

(Continued after page 72)

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KEEPING UP WITH

Digests from current literature of special importance
in diagnosis and treatment . . .

Cancer Detection In Rural Practice

Siddall reports on a cancer detection program in a rural private practice. In the course of six years, 1650 examinations were made on 950 presumably well women. In all, thirteen cancers were found: fundus of the uterus, one; breast, four; bowel, three; lymph nodes (Hodgkin's disease), one; blood (leukemia), one; skin, three. The examinees have been encouraged to have an annual physical examination, followed in six months by a pelvis-breast examination. Less than half of the examinees were 40 or more years of age, yet 84 per cent of the cancers were in this older age group.

Two hundred cytological spreads from the cervix were made according to Papanicolaou's technique, but final diagnosis of cancer depended on the biopsy. A total of 105 biopsies were taken. There were 255 benign lesions found during these examinations.

Interest in the program is indicated by the fact that the number of return visits has steadily increased each year, with a total to date of 700.

Siddall, A. C.: Cancer detection in rural practice; report of 1,650 examinations. J. A. M. A. 145: 314-317, Feb. 3, 1951.

Cytological Diagnosis in Geriatrics

The usefulness of the cytological method in the diagnosis of cancer has extended from its original application to exfoliated cells found in vaginal fluid, so that it is now of increasing value in the detection of cancers of the trachea, bronchus, lung parenchyma, kidney, bladder, prostate, esophagus,

stomach, duodenum, liver, pancreas, colon, rectum, and breast. In short, wherever there is secretion, the cytological method may be applied to determine the presence of cancer. The simplicity of collecting specimens makes the use of the method particularly adaptable to geriatric patients, and the value of the method in screening the general population of the so-called "cancer-age group" is stressed.

Seybolt, J. F.: The scope of cytology in cancer diagnosis. Geriatrics 7: 32-36, Jan.-Feb., 1952.

Carcinoma in Situ

Sixty cases of carcinoma in situ were found among 398 cases of cancer diagnosed by the vaginal smear; a total of 11,871 smears from 9748 women were made in the course of three and a half years. The initial smears from these sixty cases were diagnosed with 70 per cent accuracy—and the maximum accuracy was 82 per cent. Also, they were accurate in 54 per cent of the twenty-four showing only surface malignancy and in 81 per cent of the thirty-six cases with glandular involvement. Cervical aspirations contain more numerous cervical cells and, when submitted with a vaginal smear in a suspicious case, will often facilitate a diagnosis of cancer.

The average age of the patients was 35.2 years and a fourth of them were less than 30 years of age. Twenty patients complained of abnormal bleeding on admission; forty had leukorrhea or were asymptomatic; only 9 per cent had cervixes that bled easily on examination.

CANCER

The authors warn that a positive smear should be regarded with extreme caution and every effort should be made to confirm the diagnosis and locate the lesion before the patient is treated. A positive smear should never be considered as providing conclusive evidence of disease.

Achenbach, R. R.; Johnstone, R. E., and Hertig, A. T.: The validity of vaginal smear diagnosis in carcinoma in situ of the cervix; a report of 60 cases. Am. J. Obst. & Gynec. 61: 385-392, Feb., 1951.

Exfoliative Cytology in Industry

The authors urge that the cytological method be employed routinely in the detection of early cancer among industrial workers exposed to known carcinogenic hazards. Among workers who develop a cough, sputum studies are highly satisfactory and convenient in the detection of cancer of the lung provided reliance is not placed on a single negative or positive smear.

It is suggested that among workers exposed to aromatic amines, cytological study of urine will provide a reliable guide for the early diagnosis of cancer of the bladder and will, in large measure, serve to eliminate the need for disagreeable and painful routine cystoscopy of such workers.

Cromwell, H. A., and Papanicolaou, G. N.: Use of the cytologic method in industrial medicine; with special reference to tumors of the lung and the bladder. A.M.A. Arch. Indust. Hyg. & Indust. Med. 5: 232-233, March, 1952.

Cytology in Carcinoma in Situ

The actual incidence of carcinoma in situ is unknown, but it is being more commonly diagnosed now that the cytological technique is available. Thus, of sixty-three cervical squamous-cell carcinomas treated, in a year, on

the Gynecological Service of the University Hospitals of Cleveland, twelve (19 per cent) were intraepidermal and eleven were initially recognized by cytological examination.

It was found that specimens aspirated from the posterior fornix might contain exfoliated cells from the endometrium, cervix, vagina, and rarely from the urinary bladder; at least 10 per cent of such specimens in proved cases of carcinoma in situ failed to show tumor cells. Material obtained by scraping the cervical portio vaginalis, particularly the region of the external os, using the Ayre wooden spatula or a tongue blade, provided a concentrated specimen. It could be taken directly from a cervical erosion or other lesion. Such specimens provided recognizable cancer cells in 96 per cent of the cases of carcinoma in situ.

The author recommends submitting aspirated secretion from the cervical canal and a specimen obtained by scraping the portio. The aspirated secretion provides cells from carcinoma in situ surrounding the external os or in the cervical canal—in 80 per cent of the cases this specimen alone contained malignant-tumor cells when such a cervical lesion was present.

Reagan, J. W.: The cytological recognition of carcinoma in situ. Cancer 4: 255-260, March, 1951.

Pregnancy and Carcinoma Of the Cervix

Cervical biopsies and smears were made from 300 pregnant women without untoward effect. Among the abnormal changes seen was intraepithelial carcinoma in 0.66 per cent. The changes seen in the biopsies tended to regress within seven to twelve weeks;

the smears remained abnormal for a longer period. This points to the value of the smear as a tool in the follow-up of suspicious cases. It would seem that caution should be exercised in the final assessment and treatment of cases that during pregnancy fulfill the usual histological criteria of intraepithelial carcinoma of the cervix.

Nesbitt, R. E. L., Jr., and Hellman, L. M.: *The histopathology and cytology of the cervix in pregnancy. Surg., Gynec. & Obst.* 94: 10-20, Jan., 1952.

Sources of Mistake in Cytological Interpretation

Twenty-five cases in which intraepithelial carcinoma was diagnosed by preoperative biopsy but not confirmed by laparotomy are analyzed for their sources of error. The most common mistake leading to premature, unnecessary operation was a misinterpretation of varying degrees of basal-cell hyperactivity for genuine carcinoma *in situ*.

Patients suspected of intraepithelial carcinoma should never be treated hastily, and all cases should have repeat-biopsy confirmation. Possible confusing and mimicking lesions should be ruled out wherever possible. When biopsies are repeatedly equivocal, sharp conization of the cervix is recommended as a valuable diagnostic adjunct.

Novak, E. R., and Galvin, G. A.: *Mistakes in interpretations of intraepithelial carcinoma. Am. J. Obst. & Gynec.* 62: 1079-1085, Nov., 1951.

Ring Biopsy of the Cervix

The author states that a positive cytological test means carcinoma until proved otherwise—and great diagnostic pains must be taken before dismissing any such as a false positive. He recommends ring biopsy of the cervix in women with otherwise normal pelvic findings: A sharp knife with a narrow, angulated blade is inserted through the portio epithelium, its tip coming out in the endocervical canal; a complete circular incision is made, the ring of tissue comprising about 1 cm. of the lower end of the canal and about 1 cm.

of the surrounding portio epithelium. Bleeding is not important and hemostasis can be achieved with a hot wire cautery.

The tissue is fixed, cut into serial radial blocks, processed, and sectioned serially. Slides taken at 0.2-mm. intervals are examined so that no lesion larger than 0.2 mm. can escape detection.

After the biopsy specimen is taken, the endometrium is curetted, embedded, and examined.

Latour, J. P. A.: *Cervix ring biopsy technique. Surg., Gynec. & Obst.* 94: 270-272, March, 1952.

Results in a Cancer-Detection Center

The records of 1000 patients seen consecutively between April 14, 1948, and September 16, 1949, at the New Haven Detection Center were studied and a follow-up examination of all attempted. A one-year follow-up of 97.7 per cent was obtained and a two-year follow-up of 389 of the 1000 patients. The following pertinent facts were discovered.

Sixty-three of the 1000 patients were found to have cancer; fifty-one of these had been referred by their local physicians. Of the remaining twelve whose cancer was first suspected or discovered in the Clinic, five (0.5 per cent) were found to have symptoms that could be related to the tumor and so were not considered true detections; seven (0.7 per cent) had no symptoms related to the tumor and so were considered true detections. Of these same twelve, six occurred in 532 patients who were asymptomatic when admitted and six in 468 asymptomatic patients.

Of the patients with known cancers, a second malignant tumor was discovered in 2.6 per cent. Of the 977 patients followed for one year, seven (0.7 per cent) developed cancer during the first year; nine of the 389 followed for two years developed cancer in the second year after the initial examination.

Follow-up showed that the diagnosis was missed in two patients who appar-

ently had cancer when first examined; one was suspected of having a tumor and this was eventually proved by her physician. The other developed symptoms one month after examination and an ovarian tumor was diagnosed by her gynecologist ten months later.

Of the twelve patients in whom the tumor was discovered in the Clinic, only one had a metastatic lesion at operation. All asymptomatic patients accepted treatment as suggested. Of the sixteen patients who developed cancer after being examined in the Clinic, seven had metastatic lesions at operation. Of the seven in whom silent lesions were detected in the Clinic, six are still living two years after the Clinic examination.

The authors point out two benefits of the cancer detection center: that it plays an important public health role, since reports indicate that 50 per cent or more of the patients are referred back to local physicians for the treatment of non-neoplastic lesions; also that patients are taught to detect cancer in themselves. Thus of the nine women who developed breast cancer after being seen in the Clinic, six reported to their physicians and had radical mastectomy before the lymph nodes were involved; in three, the nodes were already involved—this is the reverse of the usual, since most women have lymph-node involvement when they come to operation. In addition, the detection centers should serve as training schools in cancer detection and should set the community standards for cancer detection.

Among methods of increasing the yield of detections, the authors point out that patients who have had one cancer are particularly good subjects for the cancer detection clinic, since the incidence of secondary carcinoma, unrelated to the first lesion is higher than the incidence of first cancer.

Clifton, E. E., and Rush, B., Jr.: The cancer detection center; its effectiveness and its role in the control of cancer, as determined by a follow-up study of 1,000 patients. Surg., Gynec. & Obst. 93: 719-726, Dec., 1951.

Detection of Nonsymptomatic Cervical Cancer

Papanicolaou smear studies were made routinely on 383 patients in a sixteen-month period by the authors, whose practice is limited to obstetrics and gynecology. A diagnosis of cancer was made in six cases, and confirmed by biopsy in five. Three of these were intraepithelial carcinoma (carcinoma in situ) and two were early invasive cancer. All five patients were less than 44 years of age, and none showed any gross lesion indicative of carcinoma on speculum examination. The authors draw attention to the probable number of early cervical cancers that are being overlooked in the office practice of both the specialist and the general practitioner who have not yet adopted the vaginal-smear technique and express a conviction that, as soon as expansion of laboratory facilities permits, the Papanicolaou smear should become an integral part of every gynecological examination carried out in office practice.

Wright, R. C., and Bristoll, D. A.: Detection of clinically unsuspected carcinoma of the cervix in office practice by the vaginal smear. Connecticut M. J. 16: 161-163, March, 1952.

Rectum, Sigmoid, and Colon Cancer Diagnosis by Cytology

The cytological method applied to rectal and colonic washings has proved to be a dependable laboratory diagnostic procedure. All patients studied were prepared by taking castor oil the previous night and cleansing enemas the morning of the examination. Even the slightest amount of fecal material was found to interfere with the reading of the slides, since the cells were shriveled.

In asymptomatic patients and those with lesions visualized by the proctoscope, the washings were obtained by a specially devised instrument. For lesions beyond the proctoscope, colon washings of about 300 to 800 cc. saline were used; an equal amount of 95 per cent alcohol was added to the return.

In all, 156 patients from the Strang

Prevention Clinic, forty-one from the Memorial Hospital Rectal Clinic, and three private patients were examined. Rectal washings were done on 178, rectal washings plus direct smears on three, colon washings on eighteen, and a direct smear only on one.

Nineteen cases of cancer were proved by biopsy or surgery; of these, smears were positive or suspicious in eighteen. The nineteenth case, first reported as a benign polyp, was later found to be a malignant polyp. There were no known false positives.

Evaluation of the cytology of the rectum, sigmoid, and ascending colon appears to be simpler than that of other organs because of the relative uniformity of the cytological picture. Malignant neoplasms can be detected early by characteristic morphological changes affecting the nucleus primarily. Benign polypoid growths may show cytohistological patterns that help to make their recognition possible at an early stage of development.

The method has particular usefulness in the diagnosis of sigmoid lesions beyond the reach of the proctoscope, particularly in cases in which the differential diagnosis between diverticulitis and early sigmoid cancer is difficult.

Bader, G. M., and Papanicolaou, G. N.: The application of cytology in the diagnosis of cancer of the rectum, sigmoid, and descending colon. Cancer 5: 307-314, March, 1952.

Early Prostatic Cancer Diagnosis by Smears

The prostatic smear can be of immeasurable help in bringing prostatic carcinoma to light in patients in whom it is not suspected clinically. Three such cases were found by smears alone in a series of seventy-two cases of prostatic carcinoma among 341 urological patients. Smears in sixty-three cases were found to have malignant cells; six others were suspicious of cancer; three at first seemed to be false negatives, but suspicious cells had been overlooked in one. Only one false positive was found among the 341 studied;

histologically this was benign prostatic hypertrophy. Half of the seventy-two cases had histological confirmation; the others were diagnosed clinically—by extension of disease to neighboring organs, elevated phosphatase values, or roentgenological evidence of metastases.

Smears were also found useful in following the course of estrogen therapy. The malignant cells degenerated or disappeared in eight of eleven cases that responded well clinically—the prostate decreased in size and a stony-hard induration changed to a softer consistency. For unknown reasons the cells did not change in three cases. On the other hand, no change occurred in the smears in seven cases that did not respond to estrogens.

Peters, H.: The prostatic smear and its clinical usefulness. J. Urol. 66: 770-777, Dec., 1951.

Sponge Biopsy in Cytology

Sponge biopsies, made endoscopically on eighty patients, were found to be particularly useful for the identification of pulmonary tumors; the differentiation between inflammatory disease and tumor; the detection of tracheal invasion by esophageal lesion in the absence of tracheal lesion, thus establishing inoperability without thoracotomy; and, on one occasion, for the identification of tumor cells from a gastric cancer with submucosal esophageal extension. Sponge biopsy produces more readable preparations than other endoscopic cytological methods.

Carter, M. G.; Nesbit, R. R., and Piper, C. A.: Endoscopic sponge biopsy. J. Thoracic Surg. 22: 386-391, Oct., 1951.

Cervical Cancer in Asymptomatic Women

Thirty-one cases of intraepithelial carcinoma of the cervix were studied in the Strang Prevention Clinic from 1948 through 1950; they were found among 10,800 new and 9500 return patients, all clinically asymptomatic for carcinoma. In most, the presence of carcinoma was first suspected from the

routine cytological smear and was subsequently confirmed by biopsy.

The average age was 46.9 years. Nine of the patients were post-menopausal; three were more than 60 years of age. Intraepithelial carcinoma was six times more common in non-Jewish than in Jewish women.

Trichomonas infection, pregnancy, estrogen therapy, and irradiation of pelvic organs may induce changes that give possible sources of error in the interpretation of cytological smear. The clinician should provide the cytologist with full information of such factors in all cases in which they are present.

Scapier, J.; Day, E., and Durfee, G. R.: *Intraepithelial carcinoma of the cervix; a cytological and clinical study.* *Cancer* 5: 315-323, March, 1952.

New Cervical Biopsy Curet

The curet has a long spiral cutting edge, with a blunt tip, so that it can be introduced into the cervical canal, and a cup at the opposite end to hold the specimen. Abundant material, untraumatized, is obtained, sufficient to enable identification of any intraepithelial cancer. Occasionally, endometrial tissue was obtained, showing that the curet penetrated the entire length of the cervical canal.

Forty-four cases of cancer were found in the specimens obtained from 400 patients. The patients included those with obvious carcinoma, those with clinically benign lesions, those with no lesions, and those in whom tissue was needed after radiation therapy in previously proved cases of carcinoma. In about one of every six cases, clinical impression was found to be wrong: in 16 per cent positive lesions had been thought to be benign and in 19 per cent negative lesions had been thought to be malignant or suspicious. This latter high figure may be due to the fact that patients with symptoms of carcinoma of the corpus, patients with previous smears reported as positive, and patients being studied for possible recurrent carcinoma were included.

Of the positive cases, thirty-two were epidermoid carcinomas, only two covert; six were carcinoma in situ, five of which were unsuspected. Twelve were adenocarcinoma, six of the cervix—three clinically malignant and three suspicious. Twelve patients were eventually found to have adenocarcinoma of the endometrium—six of which had been diagnosed by endometrial tissue obtained by the curet.

Nolan, J. F., and Budd, J. W.: *An instrument designed for biopsy of the uterine cervix.* *Cancer* 4: 1367-1371, Nov., 1951.

Cancer-Detection-Center Results

Probably the first cancer-detection clinic was organized in November, 1922, when the John Hancock Mutual Life Insurance Company made arrangements with the Collis P. Huntington Memorial Hospital, Pasadena, California. In 1937, the first well-woman clinic was established in New York, and an increasing number of cancer-detection clinics have been established since. Originally, these clinics provided a complete physical examination; later many clinics provided only special services: some limit examination to accessible sites; others to one or the other sex; others to specified ages, e.g., all those more than 30, or more than 40, years of age.

Although detection centers were originally intended for asymptomatic patients only, the incidence of cancer detected showed that many examinees did not qualify as well persons. Even those denying symptoms are apparently not a cross section of the population, since reports suggest that a common reason for seeking examination is the occurrence of cancer in other members of the family.

This evaluation of the Massachusetts demonstration covers the period May, 1948, to July, 1950. Patients were screened at the Palmer Detection Clinic by the "seven danger signals of cancer." The examination was closely confined to detection of cancerous and precancerous lesions. A few biopsies of

cervixes and of rectal polyps were taken to establish the diagnosis. Supplementary roentgenological procedures were carried out when the history or clinical findings suggested them.

Physical examination of the thorax was limited to the thoracic wall, in the belief that a routine roentgenogram was a more accurate method of revealing chest disease than even unhurried auscultation and percussion. The head and neck region was inspected carefully and the patency of the nasal passages tested. Routine roentgenological studies of the gastrointestinal tract were not done for lack of facilities. Routine sigmoidoscopic examinations were performed and an attempt made to introduce the sigmoidoscope to 25 cm. Complete urinalysis was done. The prostate gland was palpated as part of the digital rectal examination. The breasts were examined meticulously. Pelvic examination consisted of bimanual and speculum examination and the taking of a routine vaginal smear. Complete blood counts were done, but not serological examinations. A total of 890 persons were examined of whom 865 were apparently symptom-free; the others were admitted at the beginning of the study although they had symptoms; thereafter patients with symptoms were referred to their physician or a diagnostic clinic. Of the total group, 32.9 per cent were less than 40 years of age; 59.8 per cent between 40 and 60 years.

All persons seeking examination were motivated by one of three reasons: the presence of symptoms; a family history of cancer; a desire for a check-up. Of the group 30.4 per cent reported that one or both parents had had cancer.

Five cancers were found—three as a result of the initial examination. One was a Gr. III carcinoma of the cervix; another a squamous-cell carcinoma in situ of the cervix, and the third a minute focus of carcinoma in situ of the cervical stump. Two other cases were reported at the time of follow-up of the

examinees. In one, as a result of the biopsy report, the patient had been advised to have a polyp removed but procrastinated; it was removed nine months later and a minute focus of cancer found. In another no evidence of cancer was found, but a laparotomy a year later revealed cancer of the pancreas with metastases to the liver.

There were 189 persons screened out because of symptoms; 131 later came to the Palmer Diagnostic Clinic. Of these, thirteen were found to have cancer. Of those who admitted that they had sores that would not heal, 21 per cent had cancer; of those with a painless lump or thickening, 8.5 per cent had cancer; and of those with irregular bleeding or discharge, 10 per cent had cancer.

The average time spent on an individual examination was 68.6 minutes; 46.8 minutes in taking the history and performing the various examinations, the rest in filling out forms and correspondence. The Clinic secretary spent an hour in preliminary screening, making records, etc. About a half hour of nurse's and technician's time was spent in collecting specimens, making roentgenograms, etc.

It was the policy that the family physician received a report on all examinations, but 393 either did not have a family physician or preferred that he not be notified. Of this group, 112 were apparently normal; 281 had conditions warranting attention although many of the conditions were slight: epidermophytosis, ill-fitting dentures, etc.

One hundred and one recommendations for treatment were made; after 7.4 months, sixty persons were known to have had treatment; this included eight hysterectomies.

The per patient cost was found to be about \$25.00 at the detection center.

Of the patients with symptoms, the women averaged 3.2, and the men 3.9, years older than the symptom-free patients. Even taking the increase in age into account, there was a higher incidence of cancer among those with

symptoms than among those without.

The authors point out that the physician's office or a cancer-diagnosis center is the place for examination of patients with symptoms and that the physician could probably do all the examinations of the detection center provided he had proper instruments and access to hospitals for roentgenograms, etc., and provided he would allow at least an hour for the examination.

They point out that many physicians do not make pelvic and rectal examinations a part of their routine—each of which should be a part of any periodic health examination.

Lombard, H. L.; Franseen, C. C.; Snegireff, and Potter, E. A.: Report of the cancer detection center demonstration in Massachusetts. New England J. Med. 245: 793-797, No. 22, 1951.

Cytology in Diagnosis Of Early Uterine Cancer

The authors report the results of screening 6816 women, patients coming to the gynecologic out-patient clinic of Parkland Hospital, obstetric out-patients, and the entire female hospital personnel including volunteers. Of these patients, 112 (1.64 per cent) had cervical carcinoma; seventy-six (1.11

per cent) were clinically detectable while thirty-six (0.53 per cent) were unsuspected clinically. Two smears were obtained from each patient: (1) fluid was aspirated from the cervical canal with a suction pipette; (2) the squamocolumnar junction was denuded circumferentially with an Ayre spatula.

All positive cytological smears on preclinical lesions were confirmed by adequate biopsy (thirteen cases were found to be invasive).

This report emphasizes that the average age of patients with unsuspected cervical cancer was 36.6 years—but 34.6 years for those with the noninvasive, and 40.8 years for those with the invasive, carcinoma.

There were only four positive cytological smears in the seven cases of proved endometrial cancer.

The authors point out, in conclusion, that the obvious advantages of this method of screening early lesions of the cervix are partially offset by difficulties of interpretation and economic drawbacks.

Haynes, D. M.; Brown, W. W., Jr.; Hermes, R. K.; Bates, C. R., Jr., and Menger, W. F.: Cytological methods for early detection of uterine cancer. J. A. M. A. 148: 457-459, Feb. 9, 1952.

Connecticut State Detection Program

As the result of careful planning and close co-operation between the Cancer Coordinating Committee of the Connecticut State Medical Society and the Connecticut Cancer Society, a new program for "cancer detection examinations" in doctors' offices throughout the state is now officially under way. Any citizen in the State can call any Cancer Society Information Center or any County Medical Society office and obtain a list of the doctors in his area who have agreed to participate in the program. All physicians in Connecticut were provided an opportunity to be included in the list of participating physicians. The "detection examination," minimally covers the following accessible sites: lip and mouth, thyroid, breasts, skin, superficial lymph nodes, abdomen, rectum, and prostate, and a pelvic examination. There is a stool examination for blood. Additional roentgen-ray or laboratory studies may be ordered as indicated. Leaflets describing the program are being distributed throughout the State and prospective examinees are being urged to make their appointments early and at hours least likely to disturb regular office routine.



a glance . . .

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Liver-Function Tests Of Hepatic Metastases

Standard liver-function tests were performed on 160 cancer patients who did not have jaundice, including ninety-nine with proved liver metastases, to determine whether any would offer aid in the diagnosis of such metastases.

The bromsulfalein test was helpful only in those cases with hepatomegaly. The serum-alkaline-phosphatase values, however, were significantly more abnormal in patients with liver metastases: about 90 per cent of those with advanced metastatic involvement had abnormally elevated values—and 44 per cent of those cases of metastases without hepatomegaly had phosphatase values in excess of 5.4 units, the highest control value.

Mendelsohn, M. L., and Bodansky, O.: The value of liver-function tests in the diagnosis of intrahepatic metastases in the nonicteric cancer patient. Cancer 5: 1-8, Jan., 1952.

HN2 for Skin Cancers

Twenty-seven intra-arterial and fifteen intravenous injections of HN2 were given to seventeen incurable patients with far-advanced neoplastic lesions involving the skin. In all of four with mycosis fungoides there was prompt and marked improvement in those lesions that had increased vascu-

lar supply. Areas of ulceration in two of these patients healed within fourteen days after intra-arterial HN2. Of nineteen skin areas involved by various metastatic neoplastic lesions that had increased vascularity, all showed prompt decrease in size following intra-arterial HN2. Six areas without increased vascularity failed to respond.

The intra-arterial injection of HN2 is followed by less severe toxic hematological changes than intravenous injection. Those neoplastic lesions reached directly by the intra-arterial HN2 responded more promptly and completely than after intravenous HN2 in those cases in which a valid comparison could be made.

Bierman, H. R.; Kelly, K. H.; Byron, R. L., Jr.; Dod, K. S., and Shimkin, M. B.: Studies on the blood supply of tumors in man. II. Intra-arterial nitrogen mustard therapy of cutaneous lesions. J. Nat. Cancer Inst. 11: 891-905, April, 1951.

Surgery for Cervical Cancer

The current revival of interest in the surgical treatment of cancer of the uterine cervix is supported by data obtained from a review of 100 consecutive cases operated on by the author five or more years ago. Stage-I and -II cases, considered satisfactory surgical risks, were selected. A recent review of slides caused the exclusion of fifteen cases that proved to be carcinoma in

situ or endometrial cancer. All of these fifteen survived five years following radical hysterectomy with bilateral lymph-node dissection. Of the remaining eighty-five cases, the over-all survival was 74.1 per cent; forty-six were stage I with 80.7 per cent five-year survivals; and seventeen, stage II with 60.7 per cent five-year survivals. Node dissections showed carcinoma in 17.5 per cent of stage-I, and 32.1 per cent stage-II, cases.

The combination of radiation therapy and surgery is to be avoided, for this leaves a hard, frozen pelvis. Irradiation does not rid the nodes of carcinoma and is strenuous for the patient. Irradiation therapy should be studied further, for, with better knowledge of surgery, irradiation, and neoplastic growth, logical complementary attacks may be devised to the patient's advantage.

Meigs, J. V.: Radical hysterectomy with bilateral pelvic lymph node dissections. A report of 100 patients operated on five or more years ago. Am. J. Obst. & Gynec. 62: 854-865; disc. 865-870, Oct., 1951.

Chest Pathology Revealed By Mass Screening

Between April, 1949, and March, 1950, 156,724 persons in downstate Illinois, from both rural and urban populations outside of Chicago had roentgenograms of the chest. In all, 307 films (0.2 per cent) showed findings suggestive of neoplasm. Follow-up of these suspected cases yielded fourteen proved neoplasms, thirteen of which were found in persons older than 45 years. There were ten primary lung carcinomas discovered and evidence of metastatic disease was found in three. Although resectability rates are not stated and it is explained that nine of the ten primary lung cancers were advanced, the study shows the importance of mass chest x-ray screening particularly in men beyond the age of 45. The authors urge that this age group have the protection of semi-annual routine chest roentgenograms.

Gowen, G. H., and Frank, B.: Screening for chest pathology using mass x-ray survey technic. Ann. Int. Med. 36: 138-145, Jan., 1952.

Significance of Perineal Pain

A study of fourteen patients with perineal pain following abdominal perineal resection suggests a direct correlation between local recurrence resulting from perineural invasion by carcinoma and the perineal pain. Those patients in whom pain developed were all found to have recurrent carcinoma. Local recurrence would appear to be influenced by perineural invasion from the primary lesion, much as distant spread is correlated with lymphatic and venous invasion. Persistent pain in the perineal region following abdominoperineal resection is almost conclusive evidence of local recurrence of carcinoma.

Beal, J. M., and Ashley, F. L.: The significance of perineal pain following resection for carcinoma of the rectum. Surgery 30: 950-954, Dec., 1951.

Roentgenological Cure of Esophageal Cancer

The treatment of carcinoma of the esophagus by surgery or conventional irradiation results in an extremely low percentage of five-year cures. Radiotherapy of this condition has been almost abandoned because of the great technical improvements in thoracic surgery and the advent of antibiotics. However, cancer of the esophagus is almost always epidermoid and hence radiosensitive. It can be eradicated with properly planned deep roentgen-ray therapy, at least in the primary site, and an almost normal-functioning esophagus restored.

Between January 1946 and December 1950, nineteen cases of carcinoma of the esophagus were seen. Six patients were not treated owing to distant metastases or poor general condition. All of these six died within four months. Another refused treatment. Twelve were treated with deep roentgen-ray therapy. Five of these twelve, all proved epidermoid carcinomas, are living and apparently free from disease locally for periods up to fifty-two

months. The other seven of the twelve died in from three to thirty-eight months after treatment.

Of these seven, autopsies were obtained on four. Biopsies before treatment had shown all four to be epidermoid carcinomas. At the autopsies, the esophagus and surrounding tissues were carefully examined in multiple microscopic sections. No evidence of carcinoma was found in the treated area in any case. Case 1 had metastasized to gastrohepatic and periaortic nodes, and thence invaded the stomach walls, as well as to the liver, pancreas and thirteen vertebrae. Case 2 had no metastases, but tuberculosis was present. It is known that roentgen-ray therapy will activate tuberculosis, but the risk had been considered justified. Case 3 died of coronary thrombosis and showed no carcinoma of the esophagus or metastases. Case 4 had no carcinoma in lymph nodes or distant metastases. Thus cancer of the esophagus can be eradicated by proper use of deep roentgen-ray therapy.

Watson, T. A., and Brown, E. M.: X-ray therapy in carcinoma of the esophagus. J. Thoracic Surg. 23: 216-218, Aug., 1951.

Cancer of the Breast

The authors review the 787 cases, ward and private, of proved or presumed carcinoma of the breast seen in the Presbyterian Hospital, New York City, from 1935 to 1942 inclusive. Of those with primary cancer, the symptomatology could be determined accurately only on ward histories. On the 411 ward cases, the diagnosis was made during routine physical examination in 4.9 per cent; symptoms were present on admission in 92 per cent. Of these, 89.2 per cent had a tumor in the breast; 10.8 per cent had other breast symptoms: pain, enlargement, redness of skin, generalized hardness, or shrinkage of the breast—or nipple discharge, retraction, erosion, or itching or burning. Less than 5 per cent had pain and only 2 per cent had nipple discharge.

The relative operability rate of the 668 primary cases was 74.1 per cent, practically the same as for an earlier, 1915 to 1934, series. Since the present series was much more critically selected for operation, it would seem that the rate should be lowered; that it was not is probably explained because more women were coming to operation at an earlier stage in the disease.

Radical mastectomy was done in 495 primary cases; of the other 173 cases, 132 were inoperable.

Of those treated by radical mastectomy, axillary metastases were found in 56.5 per cent of those with disease of less than one month's duration; in 57.5 per cent, when of one to five months' duration; and in 68.8 per cent, when of more than six months' duration. They were found in 64.4 per cent of ward patients and in 57.9 per cent of private patients.

Local recurrence ensued in 2.6 per cent of the 190 in whom the disease was limited to the breast; in 19.3 per cent of the 305 with axillary metastases. The five-year clinical cure rates were 71.0 and 34.8 per cent respectively for these two groups.

In the age group less than 45 years, there were 50.6 per cent five-year clinical cures; 45 to 49 years, 49.3 per cent; and 50 years or more, 44.7 per cent.

Prophylactic postoperative radiation has been abandoned except in the infrequent case in which all, or almost all, of the axillary nodes are involved; it is then given to the supraclavicular and anterior mediastinal regions. Palliative radiation is being used increasingly for local recurrence and bone metastases.

The authors conclude that their earlier criteria of operability, with the possible exception of that relating to pregnancy and lactation, seem to be a reliable guide in the selection of patients for radical mastectomy.

Haugensen, C. D., and Stout, A. P.: Carcinoma of the breast. III. Results of treatment, 1935-1942. Ann. Surg. 134: 151-172, Aug., 1951.

In spite of the great advances made in the cytological diagnosis of cancer, we still have to depend on the biopsy as the most conclusive proof of cancer. A positive smear report is not a final diagnosis in itself . . . It does not eliminate the need of a careful clinical work-up and of a thorough examination of a tissue section by a qualified pathologist.

George N. Papanicolaou

The Biopsy

The importance of biopsy confirmation of positive smear tests has been repeatedly stressed. All too often, however, the specimen—whether taken for this, or for other purposes, reaches the pathologists in such a state that it is of little, if any, value to him. Here a pathologist suggests ways and means of obtaining and shipping suitable specimens.

The instruments chosen vary—scalpel, forceps with sharp biting edge, simple aspirating needle, special punch device, cutting current, swab, or spatula. All of these methods obtain tissue with different degrees of success depending upon the location of the lesion and the physician's skill — especially upon his knowing what NOT to do.

There are many NOTS: In selecting an area for biopsy, preferably take tissue from the junction between an ulcerated and a nonulcerated area and do not merely pick a bit of slough. Be generous—do not try to get the smallest bit of tissue possible.

The cutting current should be saved for biopsies that are almost the size of small surgical specimens and not used if the heat cannot be kept away from the portion of tissue to be examined. Otherwise, the tissue will be "cooked." A dull scalpel or blunt cutting forceps crushes, tears, and distorts. Crushed cells may be most confusing.

If a scalpel is used, an elliptical incision 6 to 8 mm. in length and 2 to 4 mm. in width in the center should be adequate, and it may be carried to a depth of 3 or 4 mm. If, as the incision is deepened, it is directed toward the sagittal line of the specimen, it should separate with gentle forceps traction. Do not apply forceps to the portion of tissue which is to be examined until ready for

removal. Then grasp the tissue gently and lift rather than pull it loose. Small sharp scissors may assist in separation of the specimen.

Once the specimen is secured, drying is fatal. A small specimen should be placed immediately in fixative solution. Do not put it on gauze unless the gauze is wet with either fixative or physiological saline, for the specimen will stick to the gauze and under certain conditions disappear without trace.

A larger specimen may be either placed in fixative or wrapped in saline-moist gauze and covered with waxed paper to prevent drying. If a specimen to be placed in fixative is more than a centimeter thick, make slashes in it, at intervals of 3 to 4 mm., with a knife sharp enough to cut without pressure. This allows the fixative to penetrate. The saline-moist gauze method should not be used if the specimen is to be kept more than two hours or sent to a distant laboratory. Tissues can be preserved in good condition, at least overnight, in an ordinary refrigerator if properly wrapped to prevent dehydration.

The pathologist who receives the specimen should be told the details of the case—the patient's name, age, exact source of the tissue, tentative diagnosis, whether there have been previous pathological studies and what they showed, and what significance radiological studies reveal. The opinion is widely held that all the pathologist has to do is to look at cells in order to give a sensible, useful opinion. Nothing may be farther from the truth. The pathological diagnosis of many tumors rests upon information obtained about the cases, experience, and intuition derived from lessons of the past not readily explainable to those ignorant of the art.

Present Status and Future Trends of Exfoliative Cytology

George N. Papanicolaou, M.D.

Exfoliative cytology is not a new science. It has a long history dating back to the nineteenth century. Since 1847, when Pouchet gave the first description of human vaginal smears, many secretions and fluids of the body have been explored, and many significant observations made by morphologists and pathologists interested in normal and morbid cytology and its diagnostic possibilities. Yet this impressive volume of investigative work did not reach a stage of general recognition for many decades until finally its cumulative force, strengthened by the added impact of newer contributions, caused a break in the dam of inertia and skepticism that had blocked its progressive course. It is only in the last ten years that exfoliative cytology, particularly as applied in the diagnosis of cancer, has received a wide acceptance by the medical profession, and its value and immense potentialities in diagnosis and research have been fully appreciated.

A new era in the development of exfoliative cytology was opened by the application of the vaginal-smear technique in animal experimentation, and the concomitant introduction of simpler and more effective technical procedures for the study of exfoliated cellular elements. The subsequent exhaustive study of the normal vaginal cytology, first in lower mammals and later in primates and women, formed the basis for our present cytological work. Without this thorough study of normal cells, the great variety of abnormal cell forms encountered in cancer or in other pathological conditions could not have been accurately evaluated. The lack of a thorough exploration of the normal cytology of various body fluids was probably one of the greatest handicaps to earlier investigators who centered their attention on

the study of the abnormal cell. In the same way that pathology has depended for its development on histology, so morbid cytology is fully dependent on a thorough knowledge of normal exfoliative cytology. No one should expect to be proficient in cytological diagnosis without an understanding of the normal cell and its manifold variations. In fact, in many instances, diagnosis is based equally on the evaluation of the normal as well as the abnormal exfoliated elements.

Certain technical improvements have also been contributing factors in the more recent growth of the field. Good preservation by immediate fixation is of paramount importance—and equally as necessary in the study of exfoliated cells as it is in normal and abnormal tissues. Improper fixation or drying of the smear may cause a total loss or marked distortion of the finer nuclear and cytoplasmic structural details, upon which the accurate evaluation of cells is dependent.

The development of special staining procedures for smear preparations is also of considerable importance. Good differentiation of the many exfoliated cell types, a sharp nuclear definition, and a high degree of cytoplasmic transparency are all necessary for attaining greater accuracy in the evaluation of cytological preparations. The consideration of the advantages of standardization should not discourage further efforts for the development of more effective and more specific staining procedures.

Technical improvements in the col-

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lection and handling of specimens may also result in a marked advancement in the effectiveness of certain applications. As an example, we may turn to the history of the use of the cytological method in the diagnosis of cancer of the stomach. The original difficulty in obtaining adequate material because of the digestive action of the gastric enzymes on the exfoliated elements caused a great deal of pessimism as to the future possibilities of this application. The introduction of the gastric balloon has altered the situation to the point that now this application compares in accuracy with our most dependable ones.

The cytological method is now recognized as a trustworthy tool for the diagnosis of cancer of various organs. From the standpoint of accuracy, the method is applied at present with greatest success in the diagnosis of cancer of the uterine cervix, the lung, the urinary bladder, the esophagus, the stomach, and the rectum and sigmoid colon. The wider use of the first two applications may be attributed to the simplicity of obtaining material for cytological examination as well as to the fact that they have been practiced for a much longer period of time. The detection of endometrial cancer presents greater difficulties than that of the cervix and requires greater experience and more thorough screening on the part of the diagnostician. The introduction of the endometrial smear, which is now beginning to receive wider attention, promises to furnish us with adequate material that will not only permit a more accurate diagnosis of adenocarcinoma of the endometrium but also its recognition at an earlier stage. The endometrial smear presents an additional advantage in that it occasionally contains cells that may indicate a malignant neoplasm of the ovary or tube.

In the urogenital tract we are still faced with the difficulty of obtaining adequate material for the study of certain organs such as the prostate and the kidney. Furthermore, our knowledge of the normal and abnormal cy-

tology of these organs is far from being complete. The marked cellular atypia prevailing in urine aspirated from the ureters and the pelvis of the kidney constitutes another serious handicap. However, malignant tumors developing in the transitional epithelium of the ureter or pelvis can be diagnosed with much greater accuracy than carcinomas of the parenchyma of the kidney because of the more definite cytological criteria that they exhibit and their copious exfoliation, even in the early stages of the disease. An example is offered by several cases of preinvasive carcinoma of the renal pelvis diagnosed exclusively on the basis of cytological evidence.

The microscopic examination of pleural, peritoneal, and pericardial exudates, although practiced for a longer period of time than any other cytological application, still presents problems in differential diagnosis because of the marked atypia that is often displayed by the mesothelial and histiocytic elements. However, it is justifiably in use in many laboratories today and with good results.

The cytological study of breast secretions is now beginning to receive wider attention because of its great possibilities. It gives promise of becoming valuable in the early diagnosis of intraductal papillomas and carcinomas of the breast. A limiting factor, at present, is that secretion may be obtained only in a relatively small percentage of cases.

In addition to its contribution in the diagnostic field, the cytological method seems particularly adapted to experimental and follow-up studies in problems involving prolonged study and the examination of repeated specimens. Though still limited, its use in following the effect of irradiation is bound to increase with the accumulation of data leading to a better understanding of postradiation changes as revealed in the exfoliated cells. The effect of hormonal or other therapy may also be followed closely by repeated smear examinations. In fact, the cyto-

logical method has long been utilized in the evaluation of the hormonal status as well as of changes resulting from the administration of various endocrine preparations. Furthermore, the recovery of intact cells, which this method permits, makes it particularly suitable for cytochemical and other studies related to cellular morphology and physiology. The original interest in exfoliative cytology in animal experimentation is now renewed particularly for observations on the cytological response to various carcinogenic agents.

In reviewing the present status of exfoliative cytology, it appears that its greatest contribution to science and to humanity is that it has furnished us with the means of detecting cancer in its incipency. Thus, we are provided not only with the chance of attacking cancer while it still may be amenable to treatment but also with the material for the study of its earlier developmental stages. Such material is now amply supplied by the large number of carcinomas in situ of the cervix, which are uncovered by the generalized use of this method. The thorough study of this material will lead us to the formulation of more exact criteria for early neoplastic change supplementing the well-established criteria based on the more advanced stages. The unprecedented influx of specimens from intra-epithelial lesions has created a temporary confusion that is bound to prevail until newer concepts, which will meet with general acceptance, are developed. This may come about by the combined efforts of pathologists and cytologists and the final correlation of their observations, each group following its own path of investigation, yet both working in close co-operation toward the attainment of the same final goal.

Our knowledge of the cytology as well as of the histopathology of early cancer has been derived primarily from investigation of this problem in the cervix, an organ which readily lends itself to both cytological and pathological

exploration. The cytology of the vagina and cervix has been the subject of many investigations, and there is general agreement that the early stages of cancer are characterized by distinct cytological patterns, which are in marked contrast to those prevailing in the more advanced stages.

In the latter, the malignant cells display pronounced structural modifications, nuclear as well as cytoplasmic, and tend to acquire aberrant forms or to become dedifferentiated making impossible their identification with any of the normal cell types.

The cytological changes predominating in preinvasive or early invasive carcinomas of the cervix are, as a rule, limited to the nucleus and consist chiefly in its disproportionate enlargement, irregularity in form, hyperchromatism, and bi- or multinucleation. The cancer cells as a whole show only slight changes in appearance and form and can be identified as to the epithelial cell type to which they correspond.

The term "dyskaryosis," has been suggested as appropriate for designating such abnormal changes centered in the nucleus of cells, that still retain their original well-differentiated type. Depending upon the predominance of either the endocervical cell type or of any one of the squamous varieties, the superficial, intermediate, or parabasal, one may be able to recognize a number of distinct patterns. Such patterns are often intermixed or found in conjunction with those of frank carcinomas, indicating a possible transition from the earlier to the more advanced stages. Such a transition has actually been observed in individual cases that have been followed for a long period of time thereby furnishing convincing evidence that these cytological patterns represent the earliest morphological manifestations of malignancy.

On the other hand, in recent years there has been an increasing number of observations of cases in which the abnormal cells characteristics of early cancer have disappeared indicating a spontaneous regression. Such observa-

tions have also been made in our laboratory, more particularly in cases in which the cytological picture was predominantly of the superficial cell type. It is thus possible that a different prognostic value may be attributed to the various cytological patterns. A large number of observations continued over a much longer period of time will be necessary for the clarification of these controversial points, as well as for a better understanding of reversible changes reported lately as having resulted from endocrine and other treatments.

In speaking of reversibility, one should bear in mind that this applies almost exclusively to cytological patterns. Once a biopsy is performed one can no longer be certain that the disappearance of the abnormal cells was not brought about by the surgical removal of the site of their origin. The problem of reversibility is, therefore, primarily cytological, and at the present state of our knowledge we are only justified in speaking of the reversibility of certain cytological patterns rather than that of proved early malignant lesions. One should also take into consideration the fact that not all of these abnormal patterns have been corroborated by definite pathological evidence. These points are worthy of some emphasis particularly because of the erroneous interpretation that has been given in some lay press releases. Considerable time may still elapse before we are in the position to answer whether a full regression may occur in a conclusively proved case of cancer.

Marked enlargement of cells and their nuclei, more particularly of the endocervical type, may often occur in normal pregnancy. This may be the underlying factor for the relatively frequent appearance during pregnancy of cytological and histological pictures exhibiting highly atypical cellular and nuclear forms. In some cases the atypia consists only in a cellular and nuclear hypertrophy, whereas, in others, there is hyperchromatism and other nuclear changes simulating an actual malignant

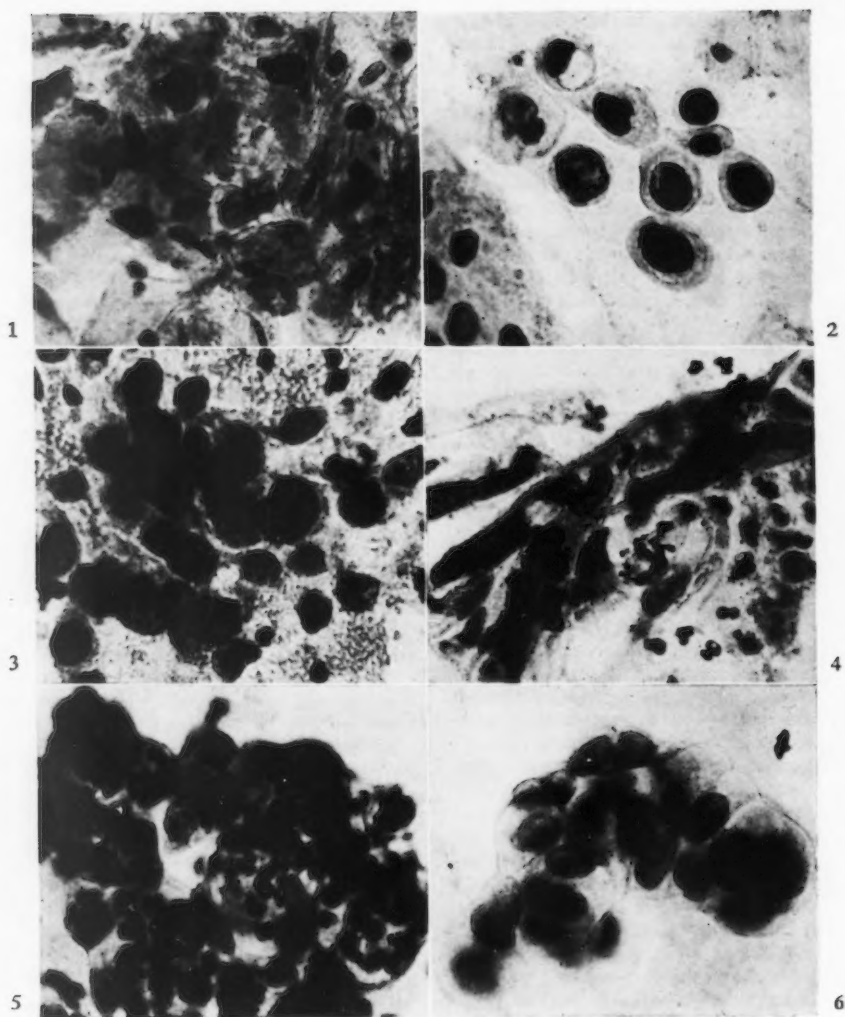
pattern. Yet, a complete regression is known to occur in some of these cases, suggesting that they may represent a rather extreme reaction to a hormonal stimulus which in turn disappears with the termination of gestation.

Regarding the future of exfoliative cytology, an optimistic outlook appears to be justified in view of recent achievements. Yet, there are still many factors that may affect its course favorably or adversely. The general attitude of the pathologists is, undoubtedly, of paramount importance. The cytological method of diagnosis of cancer is bound to become an integral part of the pathological laboratory. The recent decision of the American Board of Pathology to consider exfoliative cytology as a requirement for specialization and to include it in the Board examination for specialty certification is most gratifying and will go a long way toward directing its future course of training and giving proper guidance for its practice.

The recognition and support given to Exfoliative Cancer Cytology by the Department of Public Health, the American Cancer Society, the Commonwealth Fund, and other organizations and societies taking a special interest in cancer will have a decisive influence on its further development, its wider acceptance by the medical world, and its more appropriate use.

A cytological society, such as the Inter-Society Cytology Council now planned, could effectively assume the responsibility of formulating a program of concerted action for the solution of the problems arising from the expanding use of exfoliative cytology in the diagnosis of cancer. Such action appears to be urgently needed because of the increasing demand for cytological service and the lack of accepted standards for the regulation of its practice. It is not yet fully realized that special study and long experience are necessary prerequisites for anyone who would assume the responsibility of cytological diagnosis. No cytodiagnostic laboratory should be allowed to function without an adequately trained

(Continued on page 56)



Figures 1 to 6. Malignant cells found in smears. ($\times 600$.)

Figure 1. Superficial-cell dyskaryosis. Cervical smear. Intraepithelial carcinoma.

Figure 2. Parabasal-cell dyskaryosis. Cervical smear. Intraepithelial carcinoma.

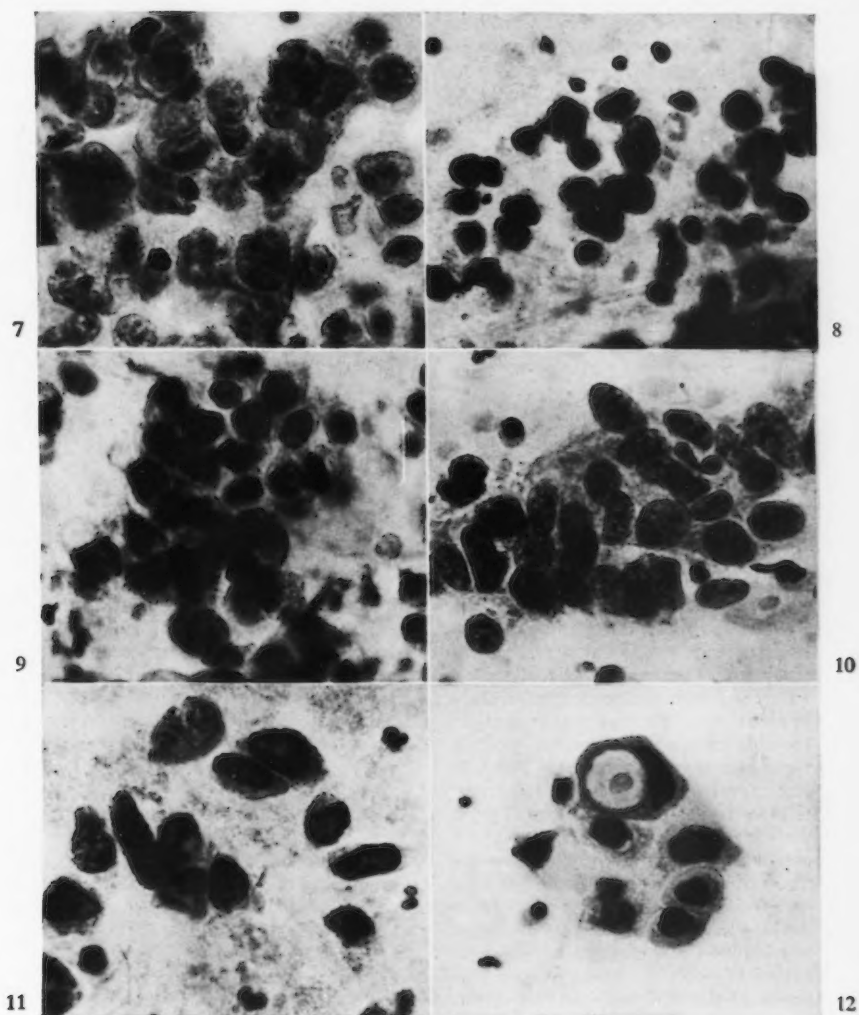
Figure 3. Endocervical-cell dyskaryosis. Cervical smear.

Following the first suspicious smear, biopsy was negative. Two years and two months later, after repeated positive smears and a second inconclusive biopsy, conization of the cervix showed an intraepithelial carcinoma with indications of very early invasion.

Figure 4. Vaginal smear. Squamous-cell carcinoma of the cervix, Grade III.

Figure 5. Vaginal smear. Adenocarcinoma of the endometrium.

Figure 6. Pleural-fluid specimen. Metastatic carcinoma of the breast.



Figures 7 to 12. Malignant cells found in smears. ($\times 600$.)

Figure 7. Sputum specimen. Bronchogenic carcinoma, pleomorphic type.

Figure 8. Sputum specimen. Bronchogenic carcinoma, anaplastic type.

Figure 9. Gastric-balloon specimen. Adenocarcinoma of the stomach, Grade II.

Figure 10. Rectal-washing specimen. Carcinoma of the rectum.

Figure 11. Voided-urine specimen. Carcinoma of the bladder.

Figure 12. Catheterized-urine specimen. Carcinoma of the prostate.

(Continued from page 53)

staff, since it would be bound to do more harm than good and discredit the method in its locality. An authoritative directory of well-qualified laboratories now in operation would be of great service to clinicians and to the public.

Despite the great strides that exfoliative cytology has made in recent years, much basic work is still needed for its continued progress toward the attainment of higher scientific standards. Of all the factors that may influence the course of its development, this need for basic contributions may be considered as the most important. A great risk lies in the fact that the value of this method as a diagnostic procedure may tend to divert future research from the purely scientific, to its more practical, aspects. Such an imbalance is already noticeable in the preponderance of papers dealing with the evaluation of diagnostic results obtained with the method, as it now stands, in contrast to those contributing to its morphological or technical advancement.

In earlier years, the cytological diagnosis of cancer was based almost exclusively on general criteria of malignancy common to all cancer cells. Only in rare instances was any attempt made to differentiate between the various types of malignant neoplasms. Now, as our experience broadens and the distinctive traits of the many malignant varieties of cells become more apparent to us, we are often able to recognize not only cancer as such, but also its specific type. It is thus possible to distinguish with a fair degree of accuracy between a squamous-cell carcinoma of the cervix and an adenocarcinoma of the endometrium; or in the lung, between an epidermoid carcinoma and an adenocarcinoma or an oat-cell carcinoma. It may even be possible to make a differential diagnosis in smears between a primary endometrial adenocarcinoma and a metastatic ovarian cystadenocarcinoma. The differentiation of the various types of neoplasms by cytological criteria acquires particular significance when

their primary site has not been ascertained.

In spite of the great advances made in the cytological diagnosis of cancer, we still have to depend on the biopsy as the most conclusive proof of cancer. A positive smear report is not a final diagnosis in itself and should not be accepted as such without further confirmation. It does not eliminate the need of a careful clinical work-up and of a thorough examination of a tissue section by a qualified pathologist.

There are, however, instances in which a confirmation of smear findings by biopsy is not possible as in lesions of organs, such as the kidney or lung, that are not easily accessible to biopsy. There are also instances when the biopsy may prove to be negative in spite of repeated positive smear findings. In such cases the responsibility falls upon the clinician who finds himself compelled to decide the course of action after weighing carefully all existing evidence, clinical, pathological and cytological. To proceed with a major operation in the absence of histopathological evidence might expose him to severe criticism. On the other hand, by ignoring positive cytological findings, he relinquishes the advantages of a possible early diagnosis and assumes the responsibility of a delay that might prove to be fatal to the patient. If cancer is to be conquered, a diagnosis at the earliest possible time is imperative.

Because of its many theoretical and practical implications, the science of the exfoliated cell has a bearing on many special fields and its development depends not only upon the contributions of the cytologists or pathologists but also upon those of clinical men representing practically every branch of medicine. Close co-operation among the cytologist, the pathologist, and the clinician is thus absolutely necessary, not only for the exploration of cytology in all its aspects, but also for the organization of any cytological laboratory that would be expected to perform its diagnostic and research functions effectively.

Cytological Techniques in Screening Uterine and Lung Cancer

Emerson Day, M.D.

"Screening" implies the survey of large numbers of asymptomatic persons to determine those who should have more extensive diagnostic examination.

The value of the screening procedure should be determined by answering two basic questions: Is it adequately reliable, and is it feasible? To be reliable, the screening method must let pass very few, if any, persons with disease — the false negatives — and should separate out for further test no more than a small number of those without actual disease — the false positives. To be feasible, a screening procedure must not entail more than an acceptable minimum inconvenience and discomfort to the examinee, and the results achieved in the detection of early disease and its cure must outweigh the cost of the screening program.

With these concepts in mind, I propose to review the experience at Strang Clinic, a large cancer-detection center, and also review certain studies of the use of cytological methods in screening for the uterus and the lung that have been reported from other centers.

Cancer of the Uterus

The three-year period from 1948 to 1950 has been selected as a reasonable sample of the Strang Clinic experience, and the results during that period have been analyzed in an attempt to evaluate the cytological-screening method for cancer of the uterus.

During this period, 16,246 women had one or more sets of screening smears. The age of this group ranged from 20 to 80 years, with more than 50 per cent of the group being between 40 and 60 years of age. All examinees were presumably well persons, although a certain number had signs or symptoms

of uterine disease when examined by the physician.

The routine procedure consisted of a smear of vaginal fluid aspirated from the posterior fornix and a smear of material obtained by cotton swab from the cervix, concentrating on the region of the external os. Any clinically suspicious areas were biopsied after the taking of smears.

TABLE I
Results of Routine Vaginal-Cervical Smears

Strang Clinic, Memorial Center,
January 1, 1948, to December 31, 1950

	Number	Rate 1000
Total women screened	16,246	—
Proved car., uterus	45	2.7
Cervix, total	36	2.2
Preinvasive	32	2.0
Invasive	4	0.2
Corpus	9	0.5

In this group of 16,246 examinees, there were forty-five proved carcinomas of the uterus (Table 1). Among the forty-five proved carcinomas of the uterus, there were thirty-six carcinomas of the cervix, all of the epidermoid or squamous type. Of these, thirty-two were preinvasive and four were early invasive epidermoid carcinomas of the cervix.

Nine carcinomas of the corpus complete the total of forty-five proved carcinomas of the uterus. These cases have been analyzed to determine the specific role of the smear in detecting the carcinoma.

In analyzing the role of the smear or

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TABLE 2
Role of Cytological Smears in Detection of 45 Carcinomas of Uterus

	Cervix		Corpus		Total	
	No.	%	No.	%	No.	%
Cases detected	36	—	9	—	45	—
CTC* essential to detection	15	42	5	55	20	44
CTC* not essential to detection	21	58	4	45	25	56

*Cytological Test for Cancer.

cytological test for cancer, indicated as CTC (Table 2), we counted as essential to detection all cases in which the smear gave us the only lead as to the presence of carcinoma. Those listed as not essential to detection by the smear method had clinical findings or history adequate to suggest biopsy or dilatation and curettage. These consisted of either erosion, contact bleeding, granularity, or suspicious areas of the cervix, a history of abnormal bleeding, or palpation of an enlarged fundus.

With that breakdown, fifteen of the thirty-six carcinomas of the cervix had no clinical reason for further diagnostic test other than the routine smear. Thus 42 per cent of the cervical cases detected depended entirely or primarily on the smear for the lead to the presence of cancer. Twenty-one, or 58 per cent, of the group, had sufficient evidence on an alert examination to have had other means of arriving at the diagnosis.

Among the nine proved carcinomas of the fundus, there were five in which there was no lead other than the smear and four in which history or physical examination would have required further test by dilatation and curettage and other procedures. Of the total of forty-

five cases of uterine cancer, twenty, or 44 per cent, were detected primarily by smear and presumably would have been missed had this not been a routine procedure.

Similar studies have been reported from two gynecological services recently. Reagan and Schmidt, of Cleveland, reported an analysis of a series of fifty-five carcinomas in which 14.5 per cent were detected primarily by the fact that the patients had had a smear as part of their routine procedure. Achenbach et al., in Boston, have reported a study in which 20 per cent were discovered primarily by Papanicolaou smears.

The higher figure — 44 per cent — at Strang Clinic is reasonable for the experience in screening asymptomatic and unselected women in contrast to patients coming to a gynecological service.

Reliability of Smears

The test of reliability of smears against final diagnosis, the classifications of the original smear in the forty-five proved cases have been tabulated (Table 3).

A certain number of our patients had many smears before arrival at final diag-

TABLE 3
Classification of Original Smear in Forty-five Proved Carcinomas of Uterus

	Cervix						Corpus		Total	
	Preinvasive		Invasive		Total					
	32		4		36		9		45	
	No.	%	No.	%	No.	%	No.	%	No.	%
Proved cases	19	59	3	75	22	61	3	33	25	55
CTC	12	38	1	25	13	36	4	45	17	38
Positive	1	3	0	0	1	3	2	22	3	7
Suspicious										
Negative										

nosis. Only the original smear, the critical first routine smear, in the standard screening procedure is analyzed in this table.

Of the thirty-two cervical preinvasive carcinomas, nineteen gave positive smears, twelve gave suspicious smears, and one gave a negative smear. Among the invasive carcinomas of the cervix there were three that gave positive smears on the original screenings, one that gave a suspicious smear, and no negatives. The total positive was 61 per cent; suspicious, 36 per cent; and false negatives, 3 per cent.

For the corpus, the smear in this small group was not as productive as in the cervix. There were only three of the group of nine, 33 per cent, that gave positive original smears; four, or 45 per cent, gave suspicious smears; and two, or 22 per cent, of this small series of corpus carcinoma, gave false-negative original screening smears.

The total figures are 55 per cent positive, 38 per cent suspicious, and 7 per cent negative.

Our invariable procedure with regard to a suspicious smear is to call the patient back immediately for repeat smears and whatever diagnostic tests are indicated, and the suspicious smear can be considered a significant finding in a screening program if handled in that way.

The relatively high proportion of false negatives in carcinoma of the fundus can be reduced by wider use of the endocervical aspiration smear, and we are making more and more use of that method of adding to the smear detection rate. There will, however, always be an irreducible minimum of a few per cent false-negative smears in uterine cancer owing to variations in the availability of cells. False-negative readings will be kept at a minimum if clinicians perfect their methods of taking smears and if pathologists report acellular or insufficient smears as, "Unsatisfactory; please repeat."

Several methods have been advocated for improving the availability of mate-

rial for cytological study by routine procedures. In our experience, the supplementing of aspiration and swabbing techniques by washing or scraping has not proved profitable in screening for uterine cancer. There are certain other centers in which these methods have been used and proved practical as a routine clinic or office procedure.

I now come to the false positive, the other side of the story, which also must be considered in evaluating screening techniques. Since this study is limited to the cases of proved carcinoma, no false positives were reported. However, during the same interval in which the forty-five proved carcinomas of the uterus were diagnosed, there were suspicious or positive smears on a number of patients who have not as yet had a histological diagnosis of carcinoma. Some of those have been lost to follow-up, and, unfortunately, we cannot give a statistical evaluation of this side of the picture. However, there are a good number of that group, in the range of thirty patients during the period of this study, who have had as many as three biopsies reported negative for cancer and are still in the process of active follow-up. We are convinced in our assumption that they have significant early disease still to be located and proved.

I believe that in this group we are dealing with that latent period we all recognize in very early carcinoma—a period that may extend to as long as three, four, or five years. During this interval our diagnostic tests, our ability to locate the focus and prove it, are not yet adequate to bring these cases into the final analysis. In some of these patients the smears continue to be suspicious or positive; in some the smears have reverted to negative.

The so-called false-positive case raises several important questions that are currently under study in the Strang Clinic and elsewhere. It is possible that a minute focus of intraepithelial carcinoma is removed in the biopsy specimen and missed in routine biopsy sections. A study of serial sections of biopsy

specimens is being undertaken to answer this question. In other words, it is possible that the biopsy is therapy and that the only focus of carcinoma is removed entirely at the time of biopsy and still missed on the usual biopsy analysis.

It is also possible that the cytological-smear technique is detecting preclinical malignant epithelial changes that are spontaneously reversible. This possibility is the basis for some of the most exciting research now developing in cancer etiology and control, and we hope that, in some symposium not too far off, this also can be analyzed.

Whatever the results of current research projects, it is certain that the patient with RELIABLY reported suspicious or positive vaginal cervical smears requires intensive diagnostic study. It is our conviction that repeatedly positive smears signify the presence of cancer at some site in the reproductive tract. Cytological findings must be confirmed by biopsy or dilatation and curettage before treatment is undertaken, but failure to confirm promptly does not lessen their significance.

One case illustrates this fact dramatically. The patient, a 52-year-old woman without complaints, had an original routine smear reported suspicious for malignancy. An immediate repeat smear was again suspicious, Papanicolaou class III, and this was followed by a series of five smears positive for malignancy class IV, and finally class V. Biopsies were reported chronic cervicitis on two occasions, negative on two occasions, and insufficient for diagnosis once. After the class-V smear, despite five negative biopsies, the patient was examined under general anesthesia and an epidermoid carcinoma of the vaginal wall posterior to the cervix was found to be the source of the malignant cells.

It must be emphasized that cytological techniques do not take the place of biopsy. All suspicious areas should be studied histologically. This series demonstrates, however, that approximately half of uterine carcinomas subsequently

proved to be present in a general screening program will be missed when conventional gynecological procedures alone are relied upon. This is because biopsy must selectively locate the site of the cancer and, in early cervical carcinoma, this may be minute or hidden. Even around-the-clock biopsies or the four-point-biopsy method advocated by Foote and Stewart may miss the focus of intraepithelial carcinoma.

The cytological study of exfoliated material brings under the microscope a collection of cells from all epithelial surfaces and greatly enlarges the potential field of examination. In the three years analyzed at Strang Clinic, routine smears added an additional twenty cases to the list of twenty-five carcinomas that could have been diagnosed by a high degree of suspicion and by the biopsy forceps and the curette alone.

Feasibility of Screening Smears

There is no doubt of the basic feasibility of vaginal cervical smears as a routine clinic or office procedure. Planned for as a regular practice, the taking of the smear adds no more than ninety seconds to the examination time and entails absolutely no additional discomfort for the patient.

We feel that the taking of smears does require a pelvic examination by a physician. I know that in some places the routine procedure has been blind aspiration by a technician, and there has been some success by this method, which would allow further extension of source material. We did have one example in which a nurse, being convinced of the importance of this procedure, took smears on herself by the simple aspiration technique and was able, in that way, to detect on herself a very early carcinoma, and such cases are a real achievement for the method done even more simply than by the full examination. However, we are committed to the idea that an adequate detection program must include a pelvic examination and that anything less than that is not adequate for the type of routine screening

that ought to be applied in practice.

Staining and reading the smears is also a reasonable undertaking, if done by trained personnel in relatively large volume. In the Strang Cytology Laboratory the average experienced technician can screen one case—that is, two slides—in ten to twelve minutes, or twenty-five to thirty cases in a reasonable working day. No accurate cost figures are available, but we estimate that the laboratory costs are in the range of \$2.50 per case screened.

Using that very rough figure, the cost of the screening smear service per case of uterine cancer detected at Strang Clinic is \$900. Since early carcinoma, the type that is detected by this screening program, is curable, we feel that that figure is well within the range of a feasible, practical procedure.

Unfortunately, the difficulty of procuring reliable reading of smears limits their use in many areas. Since smears can be mailed safely after fixation, there are no geographic limitations to extending cytological services, but there is an acute shortage of trained laboratory and professional personnel. The American Cancer Society is to be commended for its training program designed to relieve this shortage. Every effort must be made to extend this and to make reliable cytology services available at reasonable cost throughout the country.

Cytological Techniques in Lung Cancer

The use of cytological techniques in screening for lung cancer is a different matter. The value of cytology as a DIAGNOSTIC AID in early lung tumors has been amply demonstrated in many different clinics and centers throughout this country and also in Europe. Moreover, cytological studies of sputa and bronchial washes are becoming increasingly important as more patients come to diagnosis early, while tumors are small and peripheral and not available for bronchoscopic biopsy.

Watson et al. have reported a series of forty-eight patients in whom Papani-

colaou class-V sputa or bronchial washings were the only means of identifying the nature of a lung tumor preoperatively. In all forty-eight patients, carcinoma was confirmed at operation. This group considers a class-V report "the equivalent of a formal biopsy," and also finds cancer in the "vast majority" of exploratory operations of class-IV smears.

Thus, there is no question of the reliability of pulmonary cytology in the hands of trained interpreters.

On the other hand, cytological methods cannot be applied to the lung for the screening of ASYMPTOMATIC persons. They require the production of sputum or, in the absence of representative sputum specimens, intubation of the lower respiratory tract. Once obtained, the smears of bronchial washings, and of sputum particularly, require substantially more preparation in reading time than vaginal-cervical smears. In the Strang Cytology Laboratory the average screening time per case is roughly twenty minutes for washings and thirty minutes for sputum, a factor of two and three time the requirement for vaginal-cervical screening. This requirement of additional technician and cytologist time is a further limitation to the use of the method for screening purposes.

Mass screening programs for lung cancer must depend primarily upon community photoroentgen surveys and routine fluoroscopy or chest roentgenograms in physicians' offices and in hospitals. Once this initial screening for silent lung tumors has been accomplished, cytological techniques provide one of the most effective methods of establishing the nature of the lesion.

Conclusions

In conclusion, I should like to list certain concepts that we have of the role of cytology and its place in our present-day program for cancer control. The value of cytology is firmly established for routine screening for uterine cancer and for diagnostic study of lung-tumor suspects. In these two appli-

cations, cytological techniques should be adopted as widely as possible in general and specialty clinics and in office practice.

The effective use of cytology depends on the following principles:

1. A smear does not take the place of a biopsy. In practice, any suspicious area should be biopsied whether or not a smear is taken.

2. The smear can give information in regard to tissues and surfaces not practically available for biopsy. When biopsy material is unobtainable, persistently positive smears reported by reliable cytologist are presumptive evi-

dence of carcinoma. Proper action at that point must be determined for the individual case and the site implicated.

3. The false-negative smear and the false-positive smear are calculated limitations of cytology that will be reduced as we gain experience and that can be minimized by expert cytological reading and proper clinical translation of reports.

Finally, the maximum early cancer detection and prompt, proper treatment—the basis of today's cancer control—can be achieved if we have full co-operation of cytologists, pathologists, and clinicians.

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Historical Note . . .

Fifteen years before publication of the monograph on cytology in uterine cancer,¹ Papanicolaou, reporting on his still earlier work on this subject to the Third Race Betterment Conference,¹ predicted the extension of the application of his method to the diagnosis of cancer in other organs:

"Summarizing the points of importance:

"First: We have a new diagnostic method for certain malignant tumors, especially of the female genital tract.

"Second: The methods and the technique used are very simple ones, and can easily be applied in every case.

"Third: The recognition of malignancy is based not only on the presence of malignant cells but also on the reaction of the organism itself.

"Fourth: We have a better understanding of the situation in the cancer case, and we may have some help in analyzing the cancer problem in the future. In fact, I think this work will be carried a little further, and that analogous methods may be applied in the recognition of cancers in other organs. I think that some such method can be and will be developed in the future."

Nearly a quarter century later, at the Symposium on Exfoliative Cytology (October, 1951), it was amply demonstrated that his prediction had come true.

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The Gynecologist Views Cytology

Past, Present, and Future

Lewis C. Scheffey, M.D., and A. E. Rakoff, M.D.

The cytological method for the diagnosis of cancer is by no means a new technique, dating back as it does to as early as 1860, when Beale recognized neoplastic cells in the sputum from a patient with carcinoma of the pharynx.

The earliest reference of which we are aware concerning the use of the cytological method for the diagnosis of gynecological neoplasms is dated 1873, when Thomas M. Drysdale, a Philadelphian and a founding member of the American Gynecological Society, contributed a chapter to a volume of ovarian tumors by Washington L. Atlee, entitled, "Dropsical Fluids of the Abdomen; Their Physical Properties; Chemical Analysis; Microscopic Appearance and Diagnostic Value; Based on the Examination of Several Hundred Specimens." These studies by Drysdale were begun as early as 1853.

In a description of the microscopic characters of ovarian fluids, he describes "granular cells," which he considered pathognomonic for ovarian cysts, and, in addition, the presence of epithelial cells of ovarian origin. He describes also fiber-like cells in fluid of fibrocystic tumors of the uterus, and of the cellular content of amniotic fluid, and states that he had made studies on fluid from hydatid cysts, cysts of the kidney and liver, and from retained menstrual fluid. Atlee comments that rarely had he (Drysdale) failed to identify the fluid of an ovarian cyst or to distinguish it from every other kind of dropsical fluid.

Another report on the granular cell found in ovarian fluid was published by Drysdale in the "Transactions of the American Medical Association," volume 74, 1873. Drysdale encountered much opposition to his method and findings, concerning which he wrote as

follows: "In looking at the apparently barren results of numberless analyses of these organic fluids, practical men of our profession have sneered at such labors as useless; but it is hoped it will be proved in these pages that at least one point has been gained, and that in the chemical examination of these fluids, more particularly when assisted by the microscope, we have a valuable aid to diagnosis, and one nearly infallible."

Howard A. Kelly's comment in the "Dictionary of American Medical Biography" was, "unfortunately the alleged discovery did not stand the test of time as the cell was not pathognomonic."

In 1895, Rieder demonstrated mitoses in smears of ascitic fluid from a case of carcinoma of the ovary. It was not until 1928, however, that cancer cells from the genital tract were recognized in the human vaginal smear by Papanicolaou. In 1928, Babes recommended cell smears in suspected cancer of the cervix to avoid the supposed danger of biopsy. He took the material with a stiff platinum loop from the suspicious lesion, fixed the smear with alcohol, and stained it with hematoxylin and eosin. The diagnoses were based on the atypical character of the epithelial cells and proved to be right in eighteen of twenty cases of cancer of the cervix.

In 1938, Schiller also recommended scraping the surface of suspicious cervical lesions for cytological diagnosis, and R. Meyer conceded that this procedure might often furnish sufficient material on which to arrive at a positive diagnosis but questioned its general usefulness. These important preliminary observations were relatively unnoticed.

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In 1943, Papanicolaou and Traut published their classic monograph on the "Diagnosis of Uterine Cancer by the Vaginal Smear." Their observations on the value of the cytological method as a diagnostic test was promptly confirmed by Meigs and his associates and then by many others. The widespread interest in vaginal cytological preparations for the diagnosis of uterine cancer soon led to the further application of the cytological method to secretions and exudates from many other parts of the body with results that have been highly significant and valuable in many instances.

Interest in the vaginal-smear method is now quite universal, and in numerous laboratories throughout the world it has become a routine procedure. There have been several important additions made in technical detail, particularly in the collection of smears from several sources in addition to the posterior fornix of the vagina, such as the scraping of the external os of the cervix at the squamocolumnar junction, as suggested by Ayre, the aspiration of the endocervix, and, under certain circumstances, aspiration of the uterine cavity itself. Methods for concentrating cells or making sections of sedimented material or sectioning of material collected on special spongelike bases have also been advocated but have not found as wide acceptance as the simpler smear methods. The excellent methods of fixation and staining described by Papanicolaou are still most acceptable generally, although research continues on special microscopic techniques that might be more specific for neoplastic cells, such as special stains, phase microscopy, and microfluorescence.

Probably the most difficult problem in the use of the cytological technique for gynecological neoplasms has been in the establishment of criteria of malignancy. Much more difficult by cytological methods than by histological examination is the recognition of the site of origin of various cells, their wide range of normal variation, cyclic varia-

tion in association with ovarian function, changes caused by inflammatory, degenerative or irradiation effects as well as those associated with benign neoplasms. This has necessitated the training of pathologists with sufficient experience to make proper use of this technique as well as the schooling of qualified technicians who could undertake much of the preliminary screening when slides from many patients are to be examined. A number of laboratories have done pioneer work in this respect, and substantial help has come through the fellowships in exfoliative cytology sponsored and subsidized by the American Cancer Society. A good beginning in this program has been made, but much remains to be done.

As to the present, it should be said at the outset that the primary and most important step in the detection of pelvic malignancy rests upon a meticulous examination. Satisfactory illumination, utilizing the various positions suitable for adequate inspection and careful palpation, aided by few but essential instruments, mean more than simply obtaining smears from the various sites just mentioned. The cytological test was never intended to replace a thorough pelvic examination as the first requisite in cancer detection.

With the technique in its present stage of development, how, therefore, can the gynecologist best utilize the test, and what may he expect from the cytological method? This controversial problem can perhaps be discussed best by separate consideration of several of its many facets.

When Are Smears Indicated?

What are the indications for taking smears? Should every woman have a smear taken at periodic intervals? Should routine screening smears be limited to certain age groups? Should the test be a routine part of the cancer-detection examination program? Is there any point in taking smears from patients with obvious gynecological lesions or with symptoms suggestive of

cancer, or should curettage and biopsy alone be used in these patients? Should the cytological method be limited to those patients who have no apparent lesions or symptoms or to those in whom biopsy was not contemplated?

The answers to these questions are complex and probably would not be answered in the same way by various authorities in this field. There are, however, a number of available facts which may help the individual gynecologist to work out a satisfactory policy.

In the first place, the technique of taking smears is so simple that they can be taken by any physician on any patient. Furthermore, any physician anywhere can send or mail slides to one of the many centers that are now established throughout the United States and in many other parts of the world. On the other hand, there are still far too few trained pathologists and technicians available to study even a small proportion of the entire female population of the country as has been suggested in some lay articles.

So far as cost is concerned, in most centers where many smears are done the basic irreducible cost ranges at about \$1.50 to \$2.00 per patient, although the cost to the individual patient may vary from gratis to \$10 in different communities. The cost of a large screening program is therefore not inconsiderable, both in dollars and cents and in the outlay of time by pathologists and technicians.

The cost and effort of a routine screening program must be evaluated primarily by the number of unsuspected cases of carcinoma that would be discovered over and above the usual procedures ordinarily employed in careful pelvic examination. There are, as a matter of fact, but few such studies on entirely unselected cases in whom careful histories and pelvic examinations were made in addition to cytological smears.

The results of such a screening study as is being conducted in our laboratory from smears taken on unselected consecutive patients attending the health-

maintenance and cancer-detection centers in Philadelphia have been rather discouraging. In fact, they were so discouraging that the Philadelphia Division decided that they would no longer subsidize the payment for cytological smears in the routine examinations. In a four-year period during which 12,000 smears were examined on almost five thousand women, only seven patients with uterine carcinoma were discovered. The cytology test gave a correct positive or suspicious diagnosis in six of these seven cases. However, in all but one of the patients with carcinoma, a suspicious lesion was visible or symptoms were sufficiently suggestive to warrant biopsy or curettage. In only one case was the suspicion of carcinoma aroused on the basis of the smear alone. In this case it is of interest to note that the first biopsy was negative, but a repeat biopsy made after further positive smears showed an early invasive lesion of the cervix.

It might be pointed out that the Philadelphia study is not entirely representative, in that approximately 70 per cent of the women who attended the clinic were Jewish. It is well known that cervical carcinoma rarely occurs among women of this race.

In a study conducted in the Massachusetts cancer clinics by Lombard and his associates, eight symptomless carcinomas were found among 1512 patients without symptoms of gynecological disease, or one positive smear in 189 women without gynecological symptoms. It is not stated how many of these eight had observable or palpable lesions on pelvic examination. Among 1364 additional patients who presented gynecological symptoms at the time of the test, 133 positive smears were obtained, an incidence of one in ten. Eighty-nine of these positive smears were confirmed by positive biopsies, seventeen had a clinical diagnosis of carcinoma but no biopsies, and twenty-seven furnished no evidence of uterine cancer.

The results with the cytological method as a screening test in general prac-

tice are likewise quite variable. In 358 unselected women examined by a single vaginal smear, Fremont-Smith and Graham obtained six positive smears, five of which were confirmed by pathological examination—carcinoma in situ of the cervix in four and endometrial cancer in one. Of the four patients with cervical cancer, no gynecological symptoms were present in two and the cervix was normal to visualization in all. Compare these results with those of two of our colleagues. Vaginal and cervical smears were taken routinely on 2311 patients, a large proportion of whom were unselected. There were sixteen positive or suspicious reports. Unsuspected carcinoma was discovered in only two instances.

Two other groups of patients in the private practices of gynecologists on our staff are also of interest for comparison. In one there were 973 smears representing a partially selected group, many being patients with lesions or symptoms, while a minority were seen for a periodic follow-up. Not a single lesion was discovered which was entirely unsuspected and for which biopsy would not have been contemplated.

In the third group, which represented selected patients, all of whom had signs or symptoms of gynecological disturbance, there were two cases of unsuspected carcinoma in patients in whom biopsy had not been contemplated, both early squamous-cell carcinomas of the cervix.

Considerable controversy has arisen concerning the use of cytological smears in patients with visible lesions of the cervix or abnormal uterine bleeding. It has been our policy to take smears in all such cases, even those in whom biopsy or curettage was planned, in order to further academic knowledge. On a number of occasions we have had the experience of negative histological reports in patients in whom smears continued to remain positive, with subsequent repeat biopsy and discovery of carcinoma of the cervix, the endometrium, fallopian tube or ovary.

There can be little doubt that the combination of histological and cytological diagnostic procedures helps to reduce the possibility of error inherent in each method.

In the presence of lesions that are considered benign by the clinicians and in whom biopsy was not contemplated before treatment, the cytological smear adds further objective reassurance of the clinical evaluation and constitutes a record for future comparison. In this category, there fall many cases of postpartum erosions, menstrual dysfunctions in young women, and patients with fibromyomas.

The Interpretation of the Vaginal Cytological Smear

It is well known that the proper reading of cytological smears requires considerable training, experience, and judgment. The criteria of malignancy are not nearly so well established as those for histological interpretation, with the possible exception of carcinoma in situ, since controversies abound in the study of this lesion. The final interpretation not infrequently is based on the evaluation of many facts. The report that is received by the gynecologist is not often a clear-cut positive but, rather, is classified as suspicious or doubtful, or classed as I, II, III, IV, or V, indicating degrees of probability of malignancy. What the gynecologist wishes to know in such instances is whether biopsy is indicated on each of these gradations or whether further smears are desired, and a statement to this effect should accompany the report if doubt exists. In cases that remain doubtful on repeat smears, it has been our policy to advise biopsy. If the repeat smear is negative, it should be rechecked on several occasions, especially in the presence of lesions or continued symptoms. On the other hand, if the cytological smear is negative, we do not allow the report to influence our clinical impression that biopsy is indicated, for false-negative reports do occur.

Evaluation of Results

At present, the gynecologist accepts the cytological evaluation as a laboratory report that must be weighed along with the history, examination, and other findings in reaching a conclusion concerning probable diagnosis and further plan of action for each patient. The question nowadays frequently arises as to just how much significance can be attached to a positive smear, a suspicious smear, a doubtful smear, and a negative smear.

In reviewing the statistics of the accuracy of the cytological method as reported from various clinics that have had a wide experience with the method, it is at once evident that the over-all results give a degree of accuracy ranging from 95 to 98 per cent. Further analyses of the figures, however, indicate that the percentage of false positives and false negatives varies considerably in different groups. This was quite evident in the statistics presented at the round-table conference sponsored by the American Cancer Society in Boston in 1948. The false positives range from 8.7 to 25.3 per cent in different clinics, with an average of 16.4. The false negatives showed less variation, the range being from 0 to 1.2 per cent with an average of 0.7.

Collection of Smears. The patient should not douche for at least twenty-four hours before smears are taken. As a rule, the most important smear is that taken from the posterior fornix of the vagina in that it contains representative cells from all portions of the genital tract. It is apparent that the percentage of positive findings can be increased by making additional smears from the endocervix and from cervical scrapings. This was well demonstrated in two consecutive similar series of cases from our ward service.

This was an experiment we made in the beginning of the work, in which we took single smears from 500 patients who were admitted consecutively to the hospital. Then we took a second group

of 500 patients, as a control, in whom we took smears from various sites, and it increased the accuracy decidedly. We also found that we had a much lower percentage of false negatives, a reduction of from 30 to 17.6 per cent, so that we felt the multiple sites were far superior.

The Number of Smears Examined. Unquestionably the larger the number of samples taken from a patient the more accurate the result. Thus, for instance, Meigs found that in one woman known to have cancer, only six of sixteen successive smears taken in a period of seven days showed cancer cells. We have not infrequently found obviously abnormal cells on repeat smears, which could not be found on repeated re-examination of initial negative smears. It has also been noted that positives are more frequently missed in advanced lesions because of the shedding of necrotic material and bleeding than in early lesions in which the malignant cells stand out in sharp differentiation among the normal cells.

The Type of Patient Studied. The percentage of correct positives and negatives is considerably influenced by the proportion of so-called normal patients in any group. It is easier to rule out carcinoma on the basis of a perfectly normal smear than to make a diagnosis of cancer on a smear that shows many bizarre cells arising from various benign lesions. This is particularly true in smears from pregnant patients, whose cervixes reveal well-recognized physiological changes, and patients who have had previous or very recent irradiation. In our obstetrical-gynecological department we have lost the great fear that the pregnant woman should never have the cervix inspected. It is a very healthy advance in cancer detection, but we still think that it must permeate throughout the country before we even begin to pick up the vast amount of cancer of the cervix that is being reported in recent years with respect to associated pregnancies.

Excessive bleeding may also be re-

sponsible for unsatisfactory smears in positive cases. It is well established that endometrial lesions are more likely to be missed than cervical lesions, partly because of less marked cytological change and often because few cells may be present. This is especially the case in the presence of cervical stenosis, in which it is good practice to dilate the canal, if necessary, in order to insert the aspirating cannula.

The Personal Factor. There can be no question that the personal factor in the interpretation of vaginal smears plays a large part in the degree of accuracy that can be obtained. Some examiners tend to classify cells that are at all bizarre as suspicious and, as a consequence, they will have a higher percentage of false positives but very few false negatives; other workers with more rigid criteria will have the opposite experience. Thus, it is important for the gynecologist to know the criteria employed in the cytological laboratory where his slides are read.

As to the future—it has been demonstrated repeatedly that the cytology test may uncover gynecological cancer in some cases before the appearance of symptoms or signs of the disease. Furthermore, there are now numerous instances in which the cytological smear has been positive repeatedly when initial biopsy was negative. On the basis

of these qualifications alone, it seems certain that the cytological method will remain as a standard laboratory aid in the screening of patients for gynecological cancer.

On the other hand, the results of many studies plainly indicate what has been primarily stated: that the cytological method cannot replace a good gynecological history and a careful pelvic examination as definitive procedures for selecting women who should have curettage and biopsy performed. Indeed, the results suggest that the value of the cytological method is in inverse proportion to the thoroughness of the gynecological examination. Many gynecologists have been somewhat disappointed by the rarity of unsuspected cases uncovered in proportion to the many smears they have taken. Nonetheless, the fact that the over-all accuracy can be improved by a combination of careful examination plus the cytology test is the point of greatest significance.

The most urgent need for the immediate future is the adequate training of a sufficient number of pathologists and technicians to make the technique more readily available in every community.

Excellent as the Papanicolaou staining techniques are, it is to be hoped that the future may produce some new mode of examination that will even more specifically identify the cancer cell.

An Early Cytological Study

The changes in human vaginal secretion were described as early as 1847 by the French researcher, F. A. Pouchet, in his book on ovulation and other related phenomena. Unaided by modern technical methods, he could refer only to the physical properties of vaginal mucus, to fragments of epithelium, leukocytes and erythrocytes, and to decidual detritus. While he drew attention to the cyclic nature of the changes noted in these elements, there was, of necessity, no serious attention given to variations in cellular morphology.

Pouchet, F. A.: Théorie positive de l'ovulation spontanée et de la fécondation des mammifères et de l'espèce humaine, basée sur l'observation de toute la série animale. Paris. J.-B Baillière. 1847.

DOCTORS DILEMMAS

Q *A patient complains of severe epigastric pain that is worse at night and is apparently unrelieved by food or alkalis. Roentgen-ray studies of the stomach are normal and careful physical examination and laboratory studies are not revealing. The patient is not an obvious hypochondriac and I should like to urge surgical exploration.*

A Moderate to severe epigastric pain, unrelieved by food or alkalis and described as increased at night, frequently radiating to the back, and most often accompanied by weight loss, is an outstanding clinical finding in carcinoma of the pancreas. When obstructive jaundice is present, symptoms are frequently associated with cancer in the head of the pancreas. The disease is not common and results of surgical treatment have been generally disappointing, in terms of long-term survivals. It is certainly worth-while noting that one so-called "five-year survivor" following surgery for cancer of the pancreas has been reported. Exploration and appropriate surgery are imperative if results in the treatment of cancer of the pancreas are to be improved.

Q *Is nitrogen mustard (HN2) or triethylenemelamine (TEM) superior to roentgen-ray therapy in the treatment of early Hodgkin's disease?*

A If by "early" is meant circumscribed, localized Hodgkin's disease, surgery, if feasible, and/or intensive roentgen-ray therapy are the treatments of choice. The toxic, systemic effects of mustard should be avoided and immediate advantage should be taken of the opportunity, however remote, for securing local cure or con-

trol of the disease. In widespread "early" disease, oral TEM or HN2 may cause prolonged periods of improvement and radiation therapy may be directed to resistant local areas of disease.

Q *Are there truly "early" findings which might point to the existence of esophageal cancer? A patient of mine, 54 years of age, with many anxieties and a corresponding multiplicity of "symptoms," states that hiccough and a sense of substernal discomfort on swallowing have persisted over a period of six weeks. Because of their persistence, I am loath to dismiss these complaints as imaginary, although fluoroscopic examination with barium swallowing was reported normal.*

A Often very careful roentgen-ray studies will reveal small esophageal lesions that may be undisclosed by fluoroscopy. Visualization by esophagoscopy and biopsy, when feasible, will reveal early cancer of the esophagus. As for "early symptoms" of esophageal cancer, presumptively any slight disturbance in swallowing, upper gastric distress associated with pain or discomfort, regurgitation, substernal distress on swallowing, hoarseness, hiccough (recurrent, of course), or cough may indicate cancer of the esophagus, and patients sensitive enough to report these very early findings deserve every consideration in the clarification of a diagnosis. Cancer of the esophagus is rare, occurring in only about 2 per cent of alimentary-tract cancers but it should not be overlooked until the late symptoms of pronounced dysphagia, pain, and bleeding occur. It is an operable disease, amenable to treatment when localized.



new developments in cancer

Fifty-Gram Radium Beams . . .

Failla, leading American radium physicist, recently designed and installed at Roosevelt Hospital in New York a unique unit for treating cancer with radiations from 50 gm. of radium. A new principle of converging-beam therapy is used in this unit. The focused radiation from twenty-five separated 2-gm. capsules of radium sulfate gives increased effectiveness in deep-seated cancers with minimum skin damage. The only other 50-gm. radium unit is in the Institute of Cancer, Louvain, Belgium.

Twelve-Million-Volt Cancer Treatment . . .

At the Massachusetts Institute of Technology, a 12,000,000-volt Van de Graaff electrostatic generator has just been completed for nuclear atomic and cancer research, and for treatment of certain deeply located cancers. It is three times as powerful as the next most powerful in operation and will be used in conjunction with the two 2,000,000-volt generators now in operation for some time. Each of these two generators produces twice as powerful radiation as is produced by the world's entire supply of radium. A specially de-

vised chair, similar to the Bárány, rotates the patient with the deep-seated tumor always in the radiation focus, thus giving maximal effect on the tumor and minimizing the harm to overlying tissues. Of 300 cancer patients treated with the two 2,000,000-volt generators, 157 are well after twenty months.

Boron Isotope in Brain Cancer . . .

Sweet (Neurosurgeon, Massachusetts General Hospital) recently reported encouraging results from injecting intravenously boron 10, a nonradioactive isotope, in fifty-eight patients with brain cancer and exposing the brain area to neutron bombardment from an atomic pile. B^{10} is absorbed differentially, three times as much in brain cancer as in normal brain tissue. The destructive effect of neutrons on the B^{10} atom is, therefore, three times as powerful on the tumor as on normal brain tissue. More patients and longer periods of observation are required for proper evaluation of this novel therapeutic application of nuclear energy.

Cytology in Cervical Cancer . . .

To the Second National Cancer Conference, Ruth M. Graham presented a statistical study of her experience with the vaginal smear at Vincent Memorial

Laboratory, Boston, as an index of the value of cytology in diagnosis of cancer of the cervix. Among 18,302 women, 926 (5 per cent) were found to have cancer of the genital tract. Cervical cancers comprised 70 per cent, of which 13 per cent were in situ; 57 per cent of these preinvasive cancers were unsuspected. Thus cytology is proved to be of value in detecting early, symptomless, and curable cancer of the cervix.

Attack on Cancer Pain . . .

Psychotherapeutic methods, like those used to teach mothers not to fear the pain of childbirth, are being tried with some success against pain of cancer. Cobb (Massachusetts General Hospital) recently discussed the effect of cancer on the patient's mental and emotional outlook. Pain, even in cancer, is diminished when fear is eliminated. Opiates and other drugs (including radioactive gold), alcohol injections, neurectomy, lobotomy, hypnosis and psychotherapy—all have appropriate application in relief of pain from cancer.

Virus vs. Cancer . . .

Moore and her associates (Memorial Center, New York) recently found that by multiple passage through specific animal tumors, certain neurotropic viruses, with natively distinct injurious effect on sarcoma 180, could be increased in potency for this destructive capacity and decreased in neurotropic activity. Some of these potentiated viruses were found to destroy all the cells of fowl leukosis without harm to the host. Transfer of these experiments to human cancer therapy has not yet ad-

vanced to a stage to justify a statement concerning its possibilities.

Incidence of Prostatic Cancer . . .

Hudson (College of Physicians and Surgeons, Columbia University) recently screened, by biopsy, for cancer of the prostate more than one hundred inmates of a typical New York "flop-house." Contrary to the usual figure of 15 per cent incidence of prostatic cancer in men more than 50 years of age, he found 30 per cent of this group, all more than 45, had cancer of the prostate, and in 85 per cent of these the tumor was encapsulated, without metastasis, and therefore surgically curable.

New Folic Acid Antagonists . . .

Farber (Boston Children's Hospital) has found chemical compounds of the D-series to antagonize the metabolism of niacin, folic acid, and the citrovorum factor—all essential to the growth of certain forms of brain, bone, and blood cancer in mice. These new anti-vitamin substances are said to be less toxic than existing folic acid antagonists and, therefore, may prove to be of value in human leukemia.

Diet and Neoplasms . . .

Tannenbaum (Michael Reese Hospital, Chicago) recently reviewed the effects of dietary factors in the control of neoplasms. He finds much evidence to support the view that inhibition of tumor formation in animals by chronic caloric restriction may be paralleled in man. Insurance records indicate a relation between cancer mortality and body weight. For some tumor types at least, overeating and overweight are promoting influences.

G. P. and Cancer Detection

"... practicing physicians, in both small towns and large towns, should be increasingly active in programs concerned with the detection of chronic disease and in health education."

Root, H. F.: *Correspondence. New England J. Med.* 246:519, 1952.



On October 5, 1951, Dr. John J. Bittner, Director of the Division of Cancer Biology, Department of Physiology, University of Minnesota, was presented with the first Comfort Crookshank Award for Cancer Research by Sir Harold Boldero, Dean of Middlesex Hospital Medical School, London, England.

This award originated from the Comfort Crookshank Fund, a gift, during her lifetime, of the late Miss Bessie C. Crookshank. It consists of a silver medal, an honorarium, and an invitation to deliver a lecture in London. In addition, Dr. Bittner spoke before audiences at Leeds, Amsterdam, and Louvain and visited Edinburgh, Copenhagen, and Paris.

A previously postulated extra-chromosomal transmissible agent, that was later identified by Dr. Bittner, is an important, perhaps essential, factor in the genesis of breast cancer in the mouse. In his work as a geneticist, Dr. Bittner became interested in how

cancer seemed to be transmitted in certain strains of mice. Using his line of mice whose offspring would always get cancer and another strain that was highly resistant to cancer, he discovered that, when the young from mice of the high breast-cancer strain were suckled on low cancer-strain females, they usually failed to develop breast cancer—while young mice from a cancer-resistant strain developed breast cancer when nursed by high cancer-strain foster mothers. With this lead that a transmissible agent existed in the milk of mice, he was able to extract the "milk factor." Then he injected the extracted agent into mice and produced cancer. He also has shown that the ability to produce the "milk factor" can be transmitted through the male.

Dr. Bittner's research has accumulated important data that may lead to definite conclusions about the origin of cancer. The theoretical fields of the roles of heredity and of virus in cancer have been vastly stimulated by his discoveries.

Heinle (Western Reserve U.) reviewed evidence that intercurrent infection may profoundly alter the course of human leukemia. In his own experience, he stated, either pulmonary or disseminated miliary tuberculosis so changed the course of chronic and acute leukemias that there was little evidence of leukemia at autopsy.

Bierman (U. Calif.) cited experiments suggesting that white cell removal is as big a problem as white cell production in leukemia. Arterial taps and white counts in humans and in animals show that the lungs are the major site of removal of leukocytes and that they fail in this function in leukemic patients. He defined the leukemic problem as one requiring study of the production, delivery, removal and life span of leukocytes, erythrocytes and platelets and their precursors in the tissues of the body.

Law (National Cancer Institute) gave evidence that leukemia susceptibility in one strain of mouse is traceable to two chromosomes carrying marker genes for dilution and flexed-tail. He reviewed MacDowell's evidence that low leukemic mother mice can transfer resistance to offspring and that increasing parturition age of the mother was found progressively to delay the appearance of leukemia in mice. Lawrence (U. Southern California) pointed out that leukemia is about ten times as common among radiologists as among physicians in general. He said the Atomic Bomb Casualty Commission has found twenty-five leukemic deaths among 45,730 Japanese survivors who were within 2000 meters of the Nagasaki and Hiroshima bomb blasts.

Both Kirschbaum (U. Illinois) and Kaplan (Stanford U.) mentioned the part played by the thymus in the induction of leukemia. Thymectomy prevented leukemia in some susceptible animals.

Furth (Oak Ridge) asserted that a single dose of a carcinogen (like an atomic-bomb burst) under exceptional circumstances may produce human leukemia. He said repeated exposures to several carcinogens are likely causes of most cases in man.

Ross, Crockett, Finch, and Emerson (Boston U.) reported that anemia associated with leukemia and malignant lymphoma is due in most cases to red-cell destruction rather than to production failure. Actually, they reported, in many cases there is an accelerated erythrocyte production -- but not enough to keep pace with the increased destruction.

Rundles (Duke U.) reported that urethane has been found clinically useful in treatment of chronic granulocytic leukemia, multiple myeloma, and some chronic lymphocytic leukemias. Urethane suppresses cell growth differently from any other agent, inhibiting not only mitosis but also cell respiration in the absence of mitosis. At low concentrations it stimulates growth. And some abnormal plasma cells may even become dependent upon urethane.

Karnofsky (Memorial Center - New York Hospital) said that triethylenemelamine is two to three times as active by weight as nitrogen mustard when given intravenously. Orally, TEM is tolerated without nausea or vomiting. He said nitrogen mustard and TEM are particularly effective in Hodgkin's disease, lymphosarcoma, chronic myelogenous and chronic lymphatic leukemia, mycosis fungoides, and polycythemia vera.

Farber (Children's Hosp. Boston) said twenty acute leukemic children treated with anti-folic acids have survived nineteen months or longer -- one of them a 10-year-old boy still active in school and sports thirty-six months after treatment began. The lad's last remission has lasted twenty-three months.

Eliel (Okla. MRI) and Pearson (Memorial Center - New York Hosp.) said adrenal cortical atrophy often has been demonstrated in cortisone-treated patients, while others on prolonged cortisone therapy developed infections and died in collapse suggestive of acute adrenocortical hypofunction.

Haddow (Chester Beatty Group, London) introduced a new compound, GT-41, which produces remissions in from 25 to 50 per cent of chronic myelogenous leukemics. Shimkin (U. California) was enthusiastic about his first clinical tests of GT-41.

FELLOWSHIPS IN EXFOLIATIVE CYTOLOGY

The American Cancer Society sponsors fellowships in Exfoliative Cytology at thirteen medical institutions. Applicants must be graduates of Class A medical schools of the United States or Canada, citizens of the United States, not more than fifty years of age and must have completed two years of postgraduate training in pathology. Applications should be made, not to the American Cancer Society, but to the following directors at the named institutions:

George N. Papanicolaou, M.D.
Cornell University Medical College
1300 York Avenue
New York City, New York

Lewis C. Scheffey, M.D.
Jefferson Medical College Hospital
10th & Sanson Streets
Philadelphia, Penna.

Locke L. Mackenzie, M.D.
University Hospital
303 East 20th Street
New York City, New York

Warren C. Hunter, M.D.
University of Oregon Medical School
Marquam Hill
Portland, Oregon

Herbert F. Traut, M.D.
University of California Hospital
Parnassus and 3d Avenues
San Francisco, California

Otto Saphir, M.D.
Michael Reese Hospital
2839 Ellis Avenue
Chicago, Illinois

H. E. Nieburgs, M.D.
Medical College of Georgia
University Place
Augusta, Georgia

Ralph E. Kendall, M.D.
Hartford Hospital
80 Seymour Street
Hartford, Connecticut

Samuel C. Harvey, M.D.
Yale University School of Medicine
310 Cedar Street
New Haven, Connecticut

Lauren V. Ackerman, M.D.
Washington University School of Medicine
Euclid Avenue and Kingshighway
St. Louis, Missouri

Arthur T. Hertig, M.D.
Free Hospital for Women
245 Pond Avenue
Brookline, Massachusetts

John R. McDonald, M.D.
Mayo Clinic
102-110 Second Avenue, S.W.
Rochester, Minnesota

James W. Reagan, M.D.
Western Reserve University
2109 Adelbert Road
Cleveland, Ohio

Exfoliative Cytology a New Requirement

The American Board of Pathology has announced that competence in exfoliative cytology is a new requirement for specialized pathologists. In 1952, cytology will be part of the Board examination for specialty certification.

Increasing publicity is causing more women to request cytological studies as part of a gynecological examination and this fact is placing increasing emphasis on the need for pathologists to be thoroughly qualified in cytological diagnosis. Increasing interest in the application of the cytological method has led the Board to conclude that pathologists will soon be examining a tremendous number of cytological specimens. To those preparing for Board examinations, the announcement serves as a broad hint to obtain the necessary training.

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